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Consultation letters for medically unexplained physical symptoms in primary care

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Consultation letters for medically unexplained physical symptoms in primary care

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ABSTRACT

Background

In primary care between 10% and 35% of all visits concern patients with medically unexplained physical symptoms (MUPS). MUPS are associated with high medical consumption, significant disabilities and psychiatric morbidity.

Objectives

To assess the effectiveness of consultation letters (CLs) to assist primary care physicians or occupational health physicians in the treatment of patients with MUPS and diagnostic subgroups.

Search methods

We searched for randomized controlled trials (RCTs) on the Cochrane Collaboration Depression, Anxiety and Neurosis Group Controlled Trials Registers, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2009), MEDLINE (1966-2009), MEDLINE In Process (2009-08-17), EMBASE (1974-2009), PSYCINFO (1980-2009) and CINAHL (1982-2009). We screened the references lists of selected studies and consulted experts in the field to identify any additional, eligible RCTs.

Selection criteria

RCTs of CLs for patients with MUPS being treated in primary care settings.

Data collection and analysis

Two authors independently screened the abstracts of the studies identified through the searches and independently assessed the risk of bias of the included studies. We resolved any disagreement by discussion with a third review author. We assessed heterogeneity and, where a number of studies reported the same outcomes, pooled results in a meta-analysis.

Main results

We included six RCTs, with a total of 449 patients. In four studies (267 patients) the CL intervention resulted in reduced medical costs (in two studies the outcomes could be pooled: MD -352.55 US Dollars (95% CI -522.32 to -182.78)) and improved physical functioning (three studies, MD 5.71 (95% CI 4.11 to 7.31)). In two studies (182 patients) the intervention was a joint consultation with a psychiatrist in presence of the physician, and resulted in reduced severity of somatization symptoms, reduced medical consumption and improved social functioning.

Authors' conclusions

There is limited evidence that a CL is effective in terms of medical costs and improvement of physical functioning for patients with MUPS in primary care. The results are even less pronounced in patients with clinically less severe, but more meaningful, forms of MUPS and the results vary for other patient-related outcomes. All studies, except one, were performed in the United States and therefore the results can not be generalized directly to countries with other healthcare systems. Furthermore all studies were small and of only moderate quality. There is very limited evidence that a joint consultation with the patient by a psychiatrist in the presence of the physician, together with the provision of a CL, reduces severity of somatization symptoms and medical consumption.

PLAIN LANGUAGE SUMMARY

Consultation letters for use by primary care physicians in their care of patients with physical symptoms for which no organic cause can be found

In 10% to 35% of all consultations in primary care, no organic cause can be found for the physical symptoms of the patient. Patients may present with symptoms such as fatigue, headaches, dizziness, non-specific low back pain and chest pain. Such symptoms can lead to frequent consultations with the physician and high medical costs as well as causing considerable worry and disability for the patient. Patients suffering from MUPS are more likely than the average patient to experience depressive and anxiety disorders. Studies have reported positive effects of screening by a psychiatrist in the treatment of MUPS in primary care. After screening, the psychiatrist sends the primary care physician a 'consultation letter' (CL) which states the diagnosis and that patients are best helped by: 1) having their symptoms taken seriously; 2) not being told their symptoms are 'all in your head'; 3) not being referred for further investigation unless there is a clear indication of a somatic disorder; 4) undergoing a physical examination at each visit; and 5) being seen at regular intervals.

In our review we found six studies, with a total of 449 patients, in which one of two interventions were applied. One intervention (four studies, 267 patients) was a CL following a consultation between the patient and the psychiatrist; the other (two studies, 182 patients) was a CL following a joint consultation between patient, psychiatrist and primary care physician. In each case comparison was against care as usual, provided by the primary care physician. The first intervention resulted in reduced medical costs (three studies) and improved physical functioning (three studies). We found evidence for a slight reduction in the severity of the MUPS, reduced medical consumption and improved social functioning following the second intervention, although in only one of two studies assessed. There are serious limitations in generalizability of the results to modern healthcare: most trials reported doctor-related outcomes with patient-related outcomes varying in results; the intervention appears to be far more effective for the most serious but rare disorders, and less so in the more common forms of MUPS; five of the six studies were performed in the United States and four studies before 1995. Furthermore the studied populations were small and five of the six studies were of moderate quality.

Our final conclusion is that CLs may be helpful for physicians who treat patients with MUPS (based on the provider-related outcomes). However, until further studies are conducted to find out if the intervention results in improved patient-related outcomes, the overall effectiveness of CLs cannot be demonstrated.

Description of the condition

In general practice, 10% to 35% of all consultations ([Bridges](#)

BACKGROUND

1985; Escobar 1987; De Waal 2004) concern patients with medically unexplained symptoms. These patients present with physical symptoms such as fatigue, non-specific headache and non-cardiac chest pain (NCCP), for which no organic cause can be found. These symptoms are commonly described as medically unexplained physical symptoms (MUPS) (Burton 2003). If the patient attributes the symptoms to an organic cause and seeks medical help, this process is described as 'somatization'; however, MUPS is a more objective term, which is more frequently used in recent scientific literature and is more in accordance with use in primary care (Burton 2003).

There is a continuum from incidental and short-lasting MUPS, to persisting and recurrent MUPS, to a life-long history with at least 13 MUPS, which is categorized as somatization disorder according to DSM IV (APA 1994). Somatization disorder is one of the most serious and rare somatoform disorders, which is an important group of disorders in DSM IV. Other examples of somatoform disorders are conversion, body dysmorphic disorder and hypochondriasis, but these disorders are outside the scope of this review. In the continuum of severity of MUPS referred to above, the forms with more symptoms and longer lasting symptoms are associated with higher levels of disability and psychiatric comorbidity (e.g. depression and anxiety), decline in subjective health, increased healthcare utilization and a corresponding increase in costs (Bridges 1985; Escobar 1987; Craig 1993; Escobar 1998). There are several somatoform diagnostic subgroups which are used in many studies, especially abridged somatization disorder (ASD) and multisomatoform disorder (MSD). These are subthreshold forms of somatization disorder. For the diagnosis of ASD a lifetime history of four (men) to six (women) MUPS according to DSM criteria is needed (Escobar 1998), while for the diagnosis of MSD a patient needs to be affected by three current MUPS, along with a history of MUPS of at least two years (Kroenke 1997). The prevalence rates of somatization disorder, ASD and MSD differ widely with percentages of 1% to 4%, 20% and 8% in general practice populations (Gureje 1997). Because of their high prevalence, ASD and MSD are clinically most meaningful to primary care. As severity, count of symptoms and prevalence rates vary so widely, there should be caution in comparing, especially somatization disorder with ASD and MSD. Of the patients with five or more current MUPS, 50% meet the criteria for another psychiatric disorder (e.g. depression or anxiety) and 63% report psychological symptoms (Simon 1991). In 50% of cases, this psychiatric comorbidity is not recognized by the primary care physician (Bridges 1985). Primary care physicians describe patients with MUPS as difficult and time-consuming (Schilte 2000) and MUPS are also associated with a more difficult doctor-patient relationship, because the doctor and the patient hold different opinions about the causes and treatment of MUPS (Hahn 2001). Therefore, there is a need to improve adequate diagnosis and treatment of patients with MUPS. Since MUPS are associated with great reduction in subjective health and increased healthcare utilization, many studies have one or both

types of these outcomes as a primary outcome.

MUPS are also common in the occupational health setting. In many countries occupational health care is part of, or related to, primary care with regard to the counselling of employees who are on sick leave. MUPS are responsible for a considerable amount of long-term sick leave, due to disorders such as chronic fatigue syndrome, NCCP and fibromyalgia. These disorders are associated with delayed recovery, prolonged sick leave and disabilities (Eriksen 1998; Furze 2001). In most of these disorders the medical condition alone does not explain the severity of the disabilities and the duration of the sick leave (Peski 1999; Normén 2008). Sickness absence, in general, is associated with reduced well-being, a heavy socio-economic burden, and high costs (Marmot 1995). A correlation with dysfunctional health beliefs has been demonstrated, and interventions focusing on these beliefs are effective in hastening return to work (Van Tulder 2000; Petrie 2002).

Description of the intervention

Primary care physicians need effective therapeutic strategies for the treatment of MUPS (Kerwick 1997). Cognitive behavioural therapy (CBT) provided by a psychologist has been shown to be effective (Kroenke 2000), but patients with MUPS often refuse psychological or psychiatric referral for treatment. A Cochrane review showed limited evidence of effectiveness for cognitive interventions provided by general practitioners for patients with MUPS (Huibers 2003).

An alternative intervention is the consultation letter (CL). This was used for the first time in a standardized way by Smith (Smith 1986a), and later by other investigators (Rost 1994; Smith 1995; Dickinson 2003). In these studies, primary care patients were screened for multiple and recurrent MUPS by means of validated questionnaires and a structured psychiatric interview carried out by a research psychiatrist. If the diagnosis of multiple and recurrent MUPS (in a severe or less severe form, depending on the study criteria for the investigation) was confirmed, a standardized detailed CL was sent to the patient's primary care physician. Although the CL is sent to the primary care physician, it is often referred to in studies as a patient consultation letter, and this may be confusing, because the letter is not usually sent to the patient. Sometimes the letter is referred to as a 'care recommendation letter' (Dickinson 2003a), but in this review we will refer to them as CLs.

How the intervention might work

The chronic relapsing course of the disorder and its low mortality and somatic morbidity rates are described within the CL. It also contains detailed recommendations concerning management, i.e. to avoid diagnostic procedures and hospitalization, to see these patients at regular intervals and to perform a physical examination at each visit. There are three components that may contribute to

the effect of the intervention and that can explain how the intervention might work: confirmation of the diagnosis of persistent MUPS, management rules for communication and management rules for case management. Which component is the most effective, or if there is a synergetic effect is not known. In several studies (Smith 1986a; Rost 1994; Smith 1995; Dickinson 2003), this CL intervention has resulted in improved health outcomes. It is assumed that labelling symptoms as MUPS reduces the clinical uncertainty of the primary care physician and prevents potentially harmful invasive examinations and (somatic) referrals (Dickinson 2003). CLs might be an efficient method, in terms of time-saving and cost-effectiveness, for use in primary care to improve the health and well-being of patients with MUPS.

The intervention, based on the combination of screening and a CL, can be placed in the model of collaborative care, where the primary care patient is seen by a psychiatrist. The consultation is patient-centred. The primary care physician remains the responsible care-giver, but receives advice about diagnosis and treatment from the psychiatrist. This model has been reported to have favourable effects on the treatment provided by the primary care physician and on improving outcomes in patients with depression (Von Korff 1995). Collaborative care is recommended for complicated and persistent MUPS according to the review of Henningsen (Henningsen 2007), although the effects have yet to be evaluated. This intervention might overcome the reluctance of patients to psychiatric referral. This is because it has the advantage that the patient is only referred for one consultation for advice on diagnosis and treatment. There is no treatment by the psychiatrist, and the primary care physician continues as the treating physician.

Why it is important to do this review

A systematic review with regard to the intervention with patient CLs is required to assist and improve the management of patients with MUPS in primary care. Such a review has yet not been performed. Earlier systematic reviews were focused on the treatment by a psychologist, multidisciplinary treatment or pharmacological treatment and on patients with specific somatoform disorders (e.g. somatisation disorder, hypochondriasis) and certain functional disorders (e.g. chronic fatigue disorder, fibromyalgia). Furthermore, the studies included in these reviews were often centred on patients in secondary or tertiary care, limiting the generalizability to use in primary care.

OBJECTIVES

1. To assess the effectiveness of psychiatric consultation letters compared to treatment as usual for patients with MUPS in terms of symptom reduction (patient-related outcome).

2. To assess the cost-effectiveness of psychiatric consultation letters compared to treatment as usual for patients with MUPS (health-care provider-related outcome).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) concerning CLs for patients with MUPS being cared for in primary care.

We considered RCTs that randomized individual patients as well as studies that randomized clusters of patients at physician or practice level eligible for inclusion in this study. Cross-over trials were eligible for inclusion, but we took data only from the first period. We excluded data from the second period, after cross-over, because of the risk of carry-over effects.

Quasi-randomized controlled trials were not eligible for inclusion.

Types of participants

Participants must be receiving treatment in a primary care setting and have a diagnosis of multiple and recurrent MUPS, which is here defined as the presence of recent (in the past two weeks) unexplained physical symptoms, together with at least a six-month history of MUPS, and with at least three unexplained physical symptoms during the past year.

Unexplained physical symptoms were assessed with validated questionnaires, such as the SCL-90 somatization subscale (Derogatis 1977), or schedules used in a psychiatric interview, e.g. the Diagnostic Interview Schedule (DIS), which is based on the symptoms listed in the DSM-III-R (APA 1987), DSM-IV (APA 1994) or DSM-IV-TR (APA 2000).

We excluded studies if the participants were patients in a secondary and/or tertiary care setting (e.g. the medical specialist or psychiatrist is the main care-giver/ the study population is from a secondary or tertiary healthcare setting).

If the main care was provided in primary care, but the patient received additional specific care in a secondary or tertiary care setting for specific medically explained physical symptoms, these participants were eligible for inclusion.

We excluded studies if participants were children (under 18 years of age), because the prevalence of MUPS is different in children. Furthermore, the presentation of the symptoms is also determined by the parents, and various characteristics and results can not be generalized to adult patients (Postilnik 2006).

Types of interventions

The intervention must consist of a CL written by a psychiatrist and sent to a primary care physician (general practitioner or occupational health physician), concerning a patient with MUPS, in a physical one-to-one setting (between patient and physician) after screening with validated questionnaires and/or structured interviews carried out by a research assistant or a psychiatrist. The key components of the CL should be:

1. an explanation of MUPS and somatization, a description of its low mortality rate;
2. recommendations for the care of the patient;
3. recommendations for the communication with the patient.

At the very least the CL should include diagnosis (1) and either recommendations for the care of or communication with the patient (2 or 3). The CL could be a standard letter for patients with MUPS, or a patient-related document with recommendations with regard to the diagnosis of MUPS and specific recommendations within the context of this specific patient.

The advice of the psychiatrist had to be applied in a primary care setting by the primary care physician. This advice could be given in several ways, but it had at least to be written advice which was sent to the primary care physician. The advice could also be a combination of written advice and oral advice, or written advice and advice by telephone from the psychiatrist after the consultation.

We excluded studies if:

1. the treatment was not provided by the primary care physician in a face-to-face setting (e.g. group setting, by telephone, guided self-help intervention, Internet programme);
2. the treatment was provided by other disciplines (nurse, psychologist) in primary care and the results were not presented to every discipline (in such cases the role of the primary care physician was not clear);
3. there was no consultation setting with the primary care physician being the treating physician, e.g. the psychiatrist performed part or most of the treatment;
4. the patient was not seen by the psychiatrist (e.g. a consultee-centred consultation in which the patient was not seen by the psychiatrist and only the primary care physician was counselled by the psychiatrist);
5. there was no written advice from the psychiatrist (e.g. only oral advice or advice by telephone after the consultation);
6. the CL was used in both the intervention and the control group (as this would prevent assessment of the 'isolated' effects of the CL).

Types of outcome measures

Primary outcomes

We assessed the following primary outcome measures:

Health care (provider) -related

1. Use of healthcare resources/medical consumption: number of hospital days, number of medical visits, medication prescribed, etc (continuous outcome)
2. Costs of medical consumption (continuous outcome)

Patient-related

1. Severity of MUPS and somatization symptoms assessed with validated instruments such as the SCL-90 (continuous outcome) (Derogatis 1977), or during a psychiatric interview (e.g. DIS) (dichotomous outcomes).

Secondary outcomes

We assessed the following secondary **patient-related** outcome measures.

1. Sick leave and return to work: number of sick days and days until resumption of work (continuous outcome)
2. Functional status: physical, emotional and social functioning, measured with validated instruments such as sub-scales of the SF-36 (continuous outcome) (Ware 1993)
3. Perceived health: health perceptions and general health (continuous outcome)
4. Depression and anxiety measures, derived from a psychiatric interview (e.g. DIS) or validated questionnaires such as the Beck Depression Inventory (continuous outcome) (Beck 1987).

Search methods for identification of studies

Electronic searches

Searches were performed for randomized controlled trials (RCTs) on 17 August 2009 in the Cochrane Collaboration Depression Anxiety and Neurosis Group Controlled Trials Registers (CC-DANCTR References and CCDANCTR Studies), the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2009), MEDLINE, (1966-2009), MEDLINE In Process (2009-08-17), EMBASE (1974-2009), PsycINFO (1980-2009) and CINAHL (1982-2009). We retrieved all articles that cited relevant studies. There were no language restrictions.

Identification of search terms

For Medically Unexplained Physical Symptoms (MUPS) we took the search terms used by Olde Hartman 2009 in their systematic review on medically unexplained symptoms (MUS), somatization disorder and hypochondriasis, together with the top 10 functional syndromes (identified at this point in time) by Henningsen 2007. We identified additional search terms in collaboration with CC-DAN's Trials Search Co-ordinator.

For the study design we used highly sensitive RCT filters adapted from (Robinson 2002) and the Cochrane *Handbook for Systematic Reviews of Interventions* (Lefebvre 2008).

For the intervention we used terms relating to psychiatric and specialist consultation, liaison, referral, collaborative intervention, consultation letters, interdisciplinary and multidisciplinary communication and case management.

The main search strategy was not limited to treatment setting, but a complementary search for 'consultation-liaison psychiatry' was limited to primary care practice using the terms: primary health care, family practice, family physicians, general practitioners.

The complete list of search strategies performed on CENTRAL, MEDLINE and EMBASE are available in [Appendix 1](#).

CCDAN Registers

The Cochrane Collaboration Depression Anxiety and Neurosis Group (CCDAN) maintains two clinical trials registers at their editorial base in Bristol, UK: a references register and a study-based register. These registers are compiled from routine generic searches of CENTRAL, MEDLINE, EMBASE, PsycINFO, PSYINDEX, LILACS, AMED, CINAHL. Details of CCDAN's generic search strategies can be found in the 'Specialized Register' section of the [Group's module text](#). For this review, we searched the CCDAN-CTR Registers using the terms in [Appendix 2](#).

Searching other resources

Citation tracking

We scanned the reference lists of selected studies for screening to retrieve additional studies that were not identified by the electronic searches.

Personal communication

We consulted experts in the field to identify any additional, eligible RCTs (published or unpublished data).

Data collection and analysis

Selection of studies

RH and AHB independently screened the abstracts of the studies that were identified through the electronic searches. Both authors independently applied citation tracking. We resolved any disagreement about the selection of a trial by discussion among RH, AHB and the third review author (CF). In this way we established a final selection. Because some of the studies were already known to both review authors, the studies were not blinded before assessment. Trials in all languages were eligible for inclusion.

Data extraction and management

Two review authors (RH and AHB) independently extracted the study characteristics of the selected trials. We resolved any disagreement between RH and AHB by discussion among RH, AHB and CF. We extracted the following study characteristics: method, study size (number of participants in intervention and control group), age and gender of participants, number of primary care physicians, setting (e.g. general practice, occupational health organization), type of assessment of MUPS and psychiatric co-morbidity, type of intervention and type of control condition (care as usual or description of intervention in control group), allocation concealment, blinding (patients, provider, assessor), outcome measures, effect sizes, withdrawal, conclusions of the authors, and reported implications for practice.

Assessment of risk of bias in included studies

We assessed methodological quality according to The Cochrane Collaboration's Risk of Bias tool ([Higgins 2008a](#)). We added three additional criteria to the Risk of Bias checklist: assessing MUPS with validated instruments, a complete description of baseline characteristics and acceptable pre-randomization dropout (see [Figure 1](#) for more information). We judged this to be of importance for the following reasons:

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Complete description of baseline characteristics?	Were MUPS assessed with validated instruments?	Was there an acceptable pre-randomisation dropout?
Dickinson 2003	?	?	+	?	+	+	+	+	+
Katon 1992	+	?	-	?	?	+	+	+	-
Rost 1994	?	?	+	?	+	+	+	+	+
Smith 1986	+	+	+	?	+	+	+	+	+
Smith 1995	?	?	+	+	+	+	+	+	+
Van der Feltz 2006	+	+	-	+	+	-	+	+	+

- studies assess MUPS in many different ways and not always with well validated instruments;
- patients with MUPS have high prevalence rates of psychiatric co-morbidity which, together with socio-demographic characteristics, are moderators for the effectiveness of the intervention;
- results might be biased by high pre-randomization dropout because patients might be reluctant to be referred for psychiatric screening.

Therefore, the extended checklist consisted of the following internal validity criteria, with the items rated as yes, no and unclear indicating low risk of bias, high risk of bias and otherwise.

1. Generation of random allocation sequence
2. Allocation concealment
3. Blinding of patient and outcome assessor
4. Incomplete outcome data addressed
5. Free of selective reporting
6. Free of other bias
7. Complete description of baseline characteristic
8. MUPS assessed with validated questionnaires and/or structured interviews
9. Acceptable pre-randomization dropout

Measures of treatment effect

All primary and secondary outcomes were continuous, except for the psychiatric diagnoses made in a psychiatric interview (somatic disorders, depression and anxiety disorders), but these were only given as baseline characteristics. We pooled continuous data using mean differences whenever outcomes were measured using the same validated rating scales, and by using standardized mean differences where outcomes were measured with different or non-validated rating scales.

If different methods were used to measure the same continuous outcome (e.g. somatization), we extracted standard deviations from the available information. If this was not available, we calculated the value according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a). Where this was not possible, we imputed a standard error of studies with the same intervention in the same population.

Unit of analysis issues

Cluster-randomized trials

For studies with a cluster-randomized design that reported sufficient data to be included in the meta-analysis, and that did not make an allowance for the design effect, we calculated the design effect based on a fairly large assumed intra-cluster correlation of 0.05.

Because we did not expect to find information about the intra-cluster correlation for such studies, we assumed that 0.05 would be a realistic estimate, according to Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008b).

Dealing with missing data

If standard deviations were missing, we would try to calculate them by using standard errors or confidence intervals for group means. If standard deviations could not be calculated, we used average standard deviations reported by other studies for that outcome. We attempted to perform all analyses to the intention-to-treat (ITT) principle. For continuous outcomes, if studies did not present last observation carried forward (LOCF) data, we conducted available case analyses.

Assessment of heterogeneity

We assessed statistical heterogeneity using the χ^2 statistic, the associated P value and the I^2 statistic. We considered any value over 30% a possible indication of moderate heterogeneity. If we found indications of heterogeneity, we would attempt to determine the potential source, and depending on the cause, we considered an adequate strategy for dealing with heterogeneity: for example, ignoring heterogeneity, not performing the meta-analysis, or excluding a study.

Assessment of reporting biases

We did not assess for publication bias by means of funnel plots, because there were not more than 10 studies to be included in the funnel plot.

Data synthesis

If the study settings, interventions and participants were sufficiently homogeneous, we performed meta-analyses, using relative risk (RR) as the measure of effect for binary outcomes and mean difference (MD) or standardized mean difference (SMD) for continuous outcome measures.

We used a fixed-effect meta-analysis to combine the study data if trials were considered to be sufficiently similar with respect to the participants, interventions, outcome measures and timing of follow-up measurements. We used a random-effects model if the studies at issue were statistically heterogeneous.

Subgroup analysis and investigation of heterogeneity

We applied subgroup analyses if the following clinically relevant patient or intervention characteristics could be identified in an RCT.

1. Setting - general practice versus occupational health setting
2. Diagnostic criteria applied:
 - patients with MUPS in the form of somatoform disorders according to DSM-IV criteria (APA 1994) or a subthreshold somatoform disorder;
 - patients with somatoform disorders according to DSM-IV criteria (APA 1994) or patients with MUPS according to other or non-validated criteria.

Sensitivity analysis

We applied sensitivity analyses to the following key criteria and assumptions.

1. Study quality - removal of studies with low quality (based on risk of bias assessment): removal of studies with four or more items rated as high risk of bias in the quality assessment.
2. Imputation of missing data based on assumptions about outcome: imputation of standard errors from studies with the same intervention in a comparable patient population.
3. Application of Intention-to-treat (ITT) principles. For missing patients imputing data, if data were present on patient level, as if they would have completed the study.

RESULTS

Description of studies

Results of the search

The electronic searches yielded 3897 references. We screened all on title and abstract and excluded most, because the abstract made clear that the study was not a RCT, or the intervention was not a CL. Finally, we screened 31 full-text articles for eligibility, four of which we identified through personal communication with experts in the field and through tracking references. The experts we contacted also mentioned three ongoing RCTs.

Of the final 31 articles, 17 articles described 14 studies. Four secondary articles (Smith 1986b; Katon 1990; Kashner 1992; Dickinson 2003) provided additional data on four main articles that described four RCTs (Smith 1986a; Katon 1992; Rost 1994; Dickinson 2003). Of the 14 trials, six met eligibility criteria for inclusion in the review (Smith 1986; Katon 1992; Rost 1994; Smith 1995; Dickinson 2003; Van der Feltz 2006). We contacted the lead authors of these studies for additional information and

unpublished data. All but one of the authors responded to our requests, and four of them could not provide additional data because their study periods were before 1996 and the data had not been stored.

Eight of the final 14 studies did not meet inclusion criteria (Meeuwesen 1994; Carr 1997; Koopmans 1996; Barsky 2004; De Cruppe 2005; Allen 2006; Escobar 2007; Liu 2007); we excluded all of these.

Included studies

We were able to divide the included studies into two groups according to the intervention applied: four studies about separate psychiatric screening (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003) and two studies about joint consultation of the psychiatrist and primary care physician with the patient, before providing a CL (Katon 1992; Van der Feltz 2006). We have summarized the main characteristics and outcomes of the included studies in the [Characteristics of included studies](#).

Study design and length of study

The four studies which compared the CL to care as usual (CAU) all had a cross-over design (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003). We only included results from before the cross-over, because only during that period could the intervention condition be compared with the control condition. We judged that after cross-over there would be carry-over effects. Including first phase data of cross-over trials might introduce potential bias, because the report can be based on test of carry over, incomplete data from the control condition and such designs can be underpowered. However, the reports in the four studies on these topics were transparent and the risk of this kind of bias was judged to be limited. The time points for cross-over were at 12 months for three studies (Rost 1994; Smith 1995; Dickinson 2003) and at nine months for one study (Smith 1986). We considered that these time-points were sufficiently comparable. These four studies were performed in a primary care setting, and the primary care physicians were the providers of care.

In both studies comparing joint consultation to CAU there was cluster randomization. In the high-utilizers study (Katon 1992) the patients were randomized at physician level. This was the only study in which the patients were not selected for having somatization symptoms, but because they were distressed, high-utilizing patients of physicians in primary care clinics. In one study (Van der Feltz 2006) patients were randomized on practice level. In both studies the family physicians were the providers of care. The intervention condition was conducted for a period of 12 months in the Katon study and six months in the Van der Feltz study.

Intervention

In four studies (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003), the intervention group received separate psychiatric screening and only the primary care physician was provided with a CL. The contents of the CL are described in the Background section. In two studies (Katon 1992; Van der Feltz 2006), the primary care physician and a psychiatrist had a joint consultation with the patient and the CL was tailored to the patient's diagnosis. In addition, in the Van der Feltz study patients also received a letter with recommendations.

In all studies the control condition was CAU, provided by the primary care physician.

Participants

Participants were recruited from primary care. They were recruited from private and university family practices, by the physician (Smith 1986; Rost 1994; Smith 1995; Van der Feltz 2006) and also by advertisements in the local media (Rost 1994; Smith 1995). In one study (Dickinson 2003) an interviewer recruited and screened patients in the primary care clinic. In another study (Katon 1992), the patients selected were those in the top 10% of ambulatory health care visits for their age-sex group. After physicians checked potential participants against exclusion criteria, these patients were then recruited by letter and telephone.

Two studies included patients who fulfilled DSM-III criteria (Smith 1986) or DSM-III-R criteria (Rost 1994) for somatization disorder (SD). One study (Smith 1995) included patients who fulfilled criteria for abridged somatization disorder (ASD) (symptoms screened with DSM-III-R criteria). One study (Dickinson 2003) included patients who fulfilled criteria for SD, ASD and multiform somatoform disorder (MSD) (symptoms screened with DSM-III-R criteria). One study (Van der Feltz 2006) included patients who fulfilled ICD-10 criteria for somatoform disorders. One study (Katon 1992) included patients who met criteria for psychiatric distress (by fulfilling a sum score for anxiety and depression or a score for somatization) or patients who were referred by the primary care physician for a psychiatric consultation. This was the only study in which patients who did not fulfil criteria for somatization using a validated tool were also included; 20.2% of the patients fulfilled criteria for SD and 73% for ASD. The level of somatization was high in the population, but it was not specified to the diagnostic subgroups (e.g. SD, depressive disorder, anxiety disorder). Therefore, although the study fulfilled the inclusion criteria and almost three-quarters of the patients fulfilled criteria for ASD, the results of our review are also given in a subgroup analysis without this study.

Exclusion criteria were: not living within 72 kilometres of the study location (Smith 1986); in Rost 1994 and Smith 1995 they were the physician not agree to participation, no transportation to the medical centre, moving during the study and the treating physician having participated in previous studies of the authors; in Katon 1992 they were pregnancy, psychosis, dementia and patient

not known to physician. Van der Feltz 2006 employed the same exclusion criteria as Katon, and in addition excluded participants on the basis of suicidality, alcohol dependency, current psychiatric treatment, age under 18 and being unable to fill out the questionnaire. Dickinson 2003 reported no exclusion criteria.

Cultural setting and period

The studies which compared CL to CAU were performed in the United States of America (USA). Three studies were performed before 1995 (Smith 1986; Rost 1994; Smith 1995) and one study was undertaken in the past decade (Dickinson 2003). Additionally, the review authors would like to point out that there is overlap in the authors of the four studies: Smith performed two of the four studies with Rost (Rost 1994; Smith 1995) and Rost performed one study with Dickinson (Dickinson 2003).

The two studies which compared the joint consultation and CL to CAU were performed in the USA (Katon 1992) and The Netherlands (Van der Feltz 2006). The American study was performed around 1990 and the Dutch study in 2000.

Thereby five of the six studies were performed in the USA and four of the six studies were performed before 1995.

Sample size

The numbers of patients randomized into the studies varied from 38 (Smith 1986) to 251 (Katon 1992). The total number of patients included in the six studies was 449; 267 patients were included in the four studies regarding the CL; 182 patients were included in the two studies regarding the joint consultation.

Outcome measures

The primary outcomes reported in the studies were as follows.

Health care (provider)-related

Use of healthcare resources/medical consumption

This was reported in four studies (Smith 1986; Katon 1992; Smith 1995; Van der Feltz 2006). In Smith 1986, this outcome was measured by asking for information from providers and insurers of health care about hospital days and outpatient visits. In Smith 1995, the same outcomes plus data on emergency department visits were retrieved from providers and insurers of health care. In Katon 1992, this was measured by asking the provider of health care for information about primary care visits, specialty care visits, admission to inpatient medical care, radiography, laboratory testing services and prescribed medication. In one study (Van der Feltz 2006), 'medical consumption' was inventoried according to

the Visits to Doctors and Other Health Care Professionals (VD-HCP) scale, which was filled in independently by primary care physicians as well as the patients.

Medical care costs

Three studies (Smith 1986; Rost 1994; Smith 1995) all reported costs to the healthcare industry in US dollars.

Patient-related

Severity of somatization

This was reported in two studies. In one study (Katon 1992) it was measured according to the somatization scale of the Symptom Checklist Revised (SCL-R) (Derogatis 1974), and in one study (Van der Feltz 2006) with a checklist that was used in a study carried out by Speckens 1995.

The secondary outcomes (all patient-related) reported in the studies were as follows.

Mental functioning

This was reported in four studies (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003). This was measured according to the mental health subscale of the Rand Health Status Measures (Smith 1986; Rost 1994; Smith 1995) and the mental functioning subscale (MCS) of the Short Form-36 (SF-36) (Dickinson 2003). The Rand and SF-36 scales are almost identical, and can be used for comparisons.

Physical functioning

This was reported in four studies (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003). This was measured according to the physical health subscale of the Rand Health Status Measures (Smith 1986; Rost 1994; Smith 1995) and the physical functioning subscale (PCS) of the Short Form-36 (SF-36) (Dickinson 2003). Both subscales are quite comparable.

Social functioning

This was reported in four studies (Smith 1986; Rost 1994; Smith 1995; Van der Feltz 2006). It was measured in three studies according to the social functioning subscale of the Rand Health Status Measures (Smith 1986; Rost 1994; Smith 1995) and in one study (Van der Feltz 2006) according to the social interaction subscale of the Sickness Impact Profile (SIP).

Perceived health

This was measured in three studies (Smith 1986; Rost 1994; Smith 1995) according to the health perceptions subscale of the Rand Health Status Measures.

Psychiatric comorbidity

This was measured in two studies (Katon 1992; Van der Feltz 2006). In one study (Katon 1992) this was measured according to the anxiety and depression symptom scales of the Symptom Checklist Revised (SCL-R) (Derogatis 1974) and in the other study (Van der Feltz 2006) measured with the anxiety and depression scales of the Dutch translation of the Symptom Checklist-90-Revised (SCL-90-R) (Meeuwesen 1992).

Disability

This was measured in two studies (Smith 1986; Katon 1992) by rating disability days in Smith 1986 and by means of a checklist measuring chronic medical conditions and disability (Belloc 1971) in Katon 1992.

Bed days

This was measured in one study (Smith 1995).

Patient satisfaction

This was measured in one study (Smith 1986).

Excluded studies

We eventually excluded eight of the studies that we initially retrieved. In three studies (Meeuwesen 1994; Koopmans 1996; De Cruppe 2005) the study population consisted of secondary care patients and the primary care physician was not the main caregiver. In another three studies the 'isolated' effects of the CL could not be assessed (Barsky 2004; Allen 2006; Escobar 2007) because the CL had been used in the intervention group and control group (in these studies CBT was the main focus of the intervention). The Barsky study concerned patients with hypochondriasis and not MUPS. In one study the outcomes regarding somatization were not measured (Liu 2007). We excluded one study because, after obtaining the full text article, we discovered that the study design was not an RCT, but a case-control design (Carr 1997). We have summarized the excluded studies in [Characteristics of excluded studies](#).

Risk of bias in included studies

For the qualification of the risk of bias in the included studies we used the Cochrane Collaboration's Risk of Bias Tool (Higgins 2008a), amended to include three extra questions that would assess the internal validity of the studies: 1.) a complete description of baseline characteristics and 2.) an assessment of MUPS with validated instruments and 3.) acceptable pre-randomization dropout. For the criteria see Table 1. We assessed each item with yes, no or unclear, implicating low risk of bias, high risk of bias or not clear. We have provided detailed results of the assessment in the Risk of Bias tables.

Generation of random sequence

In three studies (Van der Feltz 2006, Katon 1992; Smith 1986) we found a description of an adequate method of randomization. In the three other studies (Rost 1994; Smith 1995; Dickinson 2003) we suspected an adequate method of randomization because of the mention of randomization and the equal size of the groups, but we could not find an explicit description and by contacting the authors we did not obtain an explicit answer. Therefore we rated this point as 'not clear'.

Allocation

In two studies (Smith 1986; Van der Feltz 2006) we found a description of adequate concealment of allocation. In the four other studies (Katon 1992; Rost 1994; Smith 1995; Dickinson 2003) we could not find an explicit description of any method of concealment and by contacting the authors we did not obtain an explicit answer. Therefore we rated this point as 'unclear'.

Blinding

We assessed the four studies with the CL intervention as having low risk of bias for the blinding of patients (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003). In the two studies where joint consultation was conducted, the blinding of patients was assessed as having high risk of bias (Katon 1992; Van der Feltz 2006).

We assessed all six studies as having high risk of bias for the blinding of caregivers because the caregivers in the treatment group knew about the treatment condition because they received the CL, and in two studies the psychiatrist was also present during the consultation.

We assessed all studies as having low risk of bias for the blinding of outcome assessors.

Incomplete outcome data

In three studies with the CL intervention (Smith 1986; Rost 1994; Dickinson 2003) and the joint consultation for high utilizers study

(Katon 1992), we could not clarify whether or not the results of patients who were lost to follow-up (in the Dickinson study 20%, in the other studies 7% or less) were included in the analyses. Therefore we had to rate this with unclear.

Selective reporting

In none of the six studies did we find clear indications of selective reporting: all data of intended outcome measures were present for intervention and control groups during the intervention and follow-up phases. In the high utilizers study (Katon 1992), the specific outcomes for patients with somatoform disorders were not reported, although it is likely that the data were recorded. This was rated with unclear. The focus in the study was on high utilizers with distress.

Other potential sources of bias

We found no other sources of bias in five studies. However, in one (Van der Feltz 2006) there was selection bias, because physicians decided to stop recruiting patients once they were informed that their practice was in the CAU group. Therefore, the number of participants in the intervention group was more than double than that of the control group.

Adequate description of baseline characteristics

All studies gave an adequate description of the baseline characteristics of the sample population, including psychiatric co-morbidity, sex, age and socio-economic status.

MUPS assessed with validated instruments

All studies used validated instruments and a clinical interview by psychiatrists or a research assistant to assess and verify the diagnosis of somatoform disorders for MUPS in the patients. Further to this, two studies (Katon 1992; Van der Feltz 2006) used a validated questionnaire to assess the level of MUPS.

Acceptable pre-randomization dropout

All studies except one (Katon 1992) had an acceptable pre-randomization dropout with percentages below 20%. In four studies (Smith 1986; Rost 1994; Smith 1995; Van der Feltz 2006) there was an informal process of screening by the primary care physician according clear criteria. In one study (Dickinson 2003), there was screening by the research team and in another study (Katon 1992), primary care physicians did the first part of the screening and the research team the second part.

Effects of interventions

From the included studies we evaluated the effects of two interventions: 'CL versus CAU' and 'joint consultation of patient with the psychiatrist, with the physician present, and CL versus CAU'. We pooled results of studies that evaluated the same intervention if there were sufficient data (means, standard deviations, effect sizes). We measured these results with the same instruments (e.g. in US dollars regarding costs; subscales of the RAND and SF-36 for functioning) and therefore the pooled MDs could be reported in weighted MDs. If data were available, but could not be pooled, we took a narrative approach. There were no comparable data available for the two comparisons with regard to the primary outcomes, so we could not perform meta-analysis. If in the future comparable data from further studies become available, and there is not too much heterogeneity, we think that data can be pooled for the two comparisons because the joint consultation can be clinically considered as an 'extension' of the screening by the psychiatrist before formulating the CL.

Comparison 1: CLs versus CAU

Four studies (Smith 1986; Rost 1994; Smith 1995; Dickinson 2003) with individual level RCTs compared the effect of CLs to CAU.

Primary outcomes

Health care (provider)-related

1.1 Outpatient medical consumption (outpatient visits)

For patients with ASD (Smith 1995) the intervention resulted in a non-significant difference in outpatient visits (Analysis 1.1). For patients with SD there were no significant differences in the number of outpatient visits (Smith 1986).

1.2 and 1.3 Inpatient medical consumption (emergency department visits, hospital days)

For patients with ASD (Smith 1995) the intervention resulted in a non-significant difference in emergency department visits (Analysis 1.2) and a non-significant difference in hospital days (Analysis 1.3).

For patients with SD (Smith 1986) there was a significant reduction in hospital days ($P = < 0.01$). Pooling for the outcomes of inpatient medical consumption was not possible, because of the difference in outcomes used in each study or because no standard deviations were reported (Smith 1986).

1.4 Medical costs

For patients with SD (Rost 1994) and ASD (Smith 1995) there was a reduction in medical costs in US Dollars (MD (fixed) = 352.55 (95%CI -522.32 to -182.78)) (Analysis 1.4). This is in line with the results reported by Smith 1986 (this study could not be used for pooling because Smith reported means and no standard deviations) where in the intervention condition there was a reduction of 617 US Dollar from the median base line value, mainly due to a reduction in hospital days. The reductions reported in the studies were 53% (Smith 1986), 45% (Rost 1994) and 32.9% (Smith 1995) of annual median medical charges.

Patient-related

1.5 Number and severity of somatization symptoms

The number and severity of the MUPS or somatization symptoms were not measured in the four studies during or after the intervention.

Secondary outcomes

1.6 Sick leave and return to work

There were no details about sick leave and return to work in the studies.

1.7 Functional status

We were able to sub-divide functioning into outcomes for physical, mental and social functioning as follows.

1.7.1 Physical functioning

For physical functioning (measured according to the corresponding RAND subscale) the studies concerning patients with SD (Rost 1994; Dickinson 2003), ASD (Smith 1995) and MSD (Dickinson 2003) all reported an increase in physical functioning (MD (fixed) = 5.71 (95% CI 4.11 to 7.31)) (Analysis 1.5). However it should be noted that there is an overlap between the subgroups with a SD, ASD and MSD in the Dickinson study. Because of 95.5% overlap between the MSD subgroup and the SD and ASD subgroups and comparable confidence intervals (Dickinson 2003), this will not have had any great influence on the MD and could only have decreased the MD slightly, because of the greatest effect in the SD subgroup and smaller and comparable effects in the ASD and MSD subgroups. Crucially, the baseline scores (physical functioning, mental functioning, race, age, gender, education) in the three subgroups were quite comparable (Dickinson 2003). For patients

with SD, [Smith 1986](#) reported a non-significant difference (no standard deviations reported).

1.7.2 Mental functioning

For patients with SD there was a non-significant difference in mental functioning ([Rost 1994](#)) and the same was true for patients with ASD ([Smith 1995](#)). The pooled effect resulted in a small decrease (MD (fixed) -0.66 (95% CI -2.21 to 0.9)) ([Analysis 1.6](#)). For patients with SD, [Smith 1986](#) reported a non-significant difference (no standard deviations reported).

1.7.3 Social functioning

The studies concerning patients with SD ([Rost 1994](#)) and ASD ([Smith 1995](#)) reported non-significant differences in social functioning (MD (fixed) -0.99 (95% CI -2.64 to 0.66)) ([Analysis 1.7](#)). For patients with SD, [Smith 1986](#) reported a difference of -13 ($P < 0.01$, no standard deviations reported) for the mean of the intervention condition compared to the control condition. On other scales for social functioning for patients with SD, [Rost 1994](#) reported a non-significant increase in the scale of lack or role limitations (RAND subscale).

1.8 Health perceptions

There were non-significant differences in health perceptions in the intervention condition for patients with SD ([Rost 1994](#)) and ASD ([Smith 1995](#)) (MD (fixed) -2.13 (95% CI -4.33 to 0.08)) ([Analysis 1.8](#)). In the other study with patients with SD ([Smith 1986](#)), there was no difference in perceived health after the intervention period. Because [Smith](#) reported no standard deviations, this outcome could not be used for pooling.

1.9 Depression and anxiety measures

Psychiatric comorbidity

There were no details about the effects on psychiatric comorbidity in the studies.

1.10 Other outcomes

Disability

One study ([Smith 1986](#)) for patients with SD disorder reported a non-significant difference of disability days for the patients in the intervention condition.

Bed days

For patients with ASD, [Smith 1995](#) reported a non-significant difference of bed days.

Patient satisfaction

For patients with SD, [Smith 1986](#) reported no changes in patient satisfaction.

Comparison 2: Joint consultation of psychiatrist and physician and consultation letter versus CAU

Primary outcomes

In two studies ([Katon 1992](#); [Van der Feltz 2006](#)), one of which was a cluster level RCT ([Van der Feltz 2006](#)), the intervention concerned a joint consultation of the patient with the psychiatrist in presence of the physician, followed by a CL. The two studies could not be pooled because [Katon 1992](#) did not provide detailed information about standard deviations. In the only study ([Van der Feltz 2006](#)) with cluster randomization, there was such a low variance between primary care physician practices (0.117) that we considered correction for the design effect not necessary in the meta-analysis.

Health care (provider)-related

2.1 Primary care medical consumption

There was a reduction in the use of health care in general practices in the patient group with SD ([Van der Feltz 2006](#)) (MD (fixed) -9.85 (95% CI -15.19 to -4.52)) ([Analysis 2.1](#)). In the patient group of distressed high utilizers ([Katon 1992](#)), there were no significant differences in primary care, radiography and laboratory testing services between the intervention and control group. In this second study, the only significant effect was seen in the percentage of intervention patients who used an antidepressant, longer-term use of antidepressants and percentage of rate of prescribing antidepressants by the 'intervention physicians'.

2.2 Total health care medical consumption

There was a reduction in use of total health care in the patient group with somatoform disorders ([Van der Feltz 2006](#)) (MD (fixed) = -95.97 (95% CI -148.71 to -43.23)) ([Analysis 2.2](#)). For the patient group of distressed high utilizers ([Katon 1992](#)) there were non-significant effects for specialist care visits, admission to inpatient medical care, radiography and laboratory testing services.

Patient-related

2.3 Severity of somatization symptoms

Van der Feltz 2006 reported a reduction of somatization symptom severity (SCL-90) in the patient group with different kinds of somatoform disorders (Analysis 2.3). Katon 1992 reported for a group of distressed high utilizers, in which 73% fulfilled the criteria for ASD, non-significant differences (no details) for somatization symptoms.

Secondary outcomes

2.4 Functional status

2.4.1 Social functioning

There was a significant improvement in social functioning in the patient group with somatoform disorders (measured with the subscale of the Sickness Impact Profile) (Van der Feltz 2006) (Analysis 2.4). There was a non-significant change in disability in the group of distressed high utilizers (Katon 1992).

2.5 Depression and anxiety measures

Psychiatric comorbidity

Both studies reported non-significant changes in psychiatric comorbidity.

Subgroup analysis

Effects of CL in SD versus ASD and MSD

We used the results of Comparison 1 for this subgroup analysis. Health care (provider) related outcomes were reported on primary outcomes only. For patients with SD (Rost 1994) and ASD (Smith 1995), there was a reduction in medical costs in US dollars (MD (fixed) 352.55 (95% CI -522.32 to -182.78)) (Analysis 1.4). The reductions reported in the studies were 45% for patients with SD (Rost 1994) and 32.9% for patients with ASD (Smith 1995) of annual median medical charges.

Patient-related outcomes were reported on secondary outcomes only. For physical functioning, the strongest improvement was achieved in patients with SD (Rost 1994; Dickinson 2003) (MD (fixed) 7.57 (95% CI 4.04 to 11.09)) compared to patients with

MSD (Dickinson 2003) (MD (fixed) 5.50 (95% CI 2.45 to 8.55)) and ASD (Smith 1995; Dickinson 2003) (MD (fixed) 5.07 (95% CI 2.81 to 7.33)) (Analysis 1.5). For mental functioning, social functioning and health perceptions there were non-significant changes (except mental health in patients with SD (Rost 1994) - a reduction) in the diagnostic subgroups.

Effects of joint consultation and CL in patients with somatoform disorders versus patients with distressed high utilizers

The distressed high utilizers study (Katon 1992) reported non-significant changes for the primary outcomes of somatization (SCL scale) and medical consumption (doctor visits, laboratory testing, radiography). This was also the case for the secondary outcomes mental health (SCL depression, SCL anxiety) and disability. Therefore the results of Comparison 2 can be used, which showed only significant results in one study (Van der Feltz 2006): a reduction of severity of somatization symptoms, primary care and total healthcare consumption and an improvement in social functioning in patients with somatoform disorders.

In our protocol we listed the following issues that could be relevant.

- Differences between patients from general practice versus occupational health practice: there were no studies carried out in occupational health settings.
- Differences between patient groups with a SD, ASD and MSD for one outcome. For the intervention 'CL versus CAU', the reduction in medical costs was stronger in patients with a SD, than in patients with ASD, as was the improvement in physical functioning.
- Differences between patient groups with diagnosed somatoform disorders versus all other forms of MUPS: this analysis added nothing to the conclusions about the effectiveness of the joint consultation.

Sensitivity analysis

Effects of CL in SD versus ASD and MSD for medical costs and physical functioning with imputed data for one study with SD

Of the primary outcomes medical costs and physical symptoms, we could not pool for one study (Smith 1986) because no standard deviations were reported. According to our protocol we used the outcomes of the two other studies reporting results on these outcomes for patients with SD (Rost 1994; Dickinson 2003). For medical costs we imputed the SE from one study (Rost 1994) and for physical functioning we imputed a pooled SE from both studies. For medical costs, after imputing the SE, the pooled reduction in US dollars was 422.36 (MD (fixed) (95% CI -568.01 to -276.71), with the reduction in patients with SD being 541.50 (MD (fixed) (95% CI -741.96 to -341.04)) and in patients with ASD 289.11

(MD (fixed) (95% CI -501.10 to -77.12)). See [Analysis 3.1](#). For physical functioning, after imputing of the pooled SE, the pooled improvement was 3.57 (MD (fixed) (95% CI 2.07 to 5.07), with the improvement in patients with SD being 0.02 (MD (fixed) 95% CI -2.64 to 2.68), in patients with ASD 5.07 (MD (fixed) 95% CI 2.81 to 7.33) and MSD 5.50 (MD (fixed) 95% CI 2.45 to 8.55). See [Analysis 3.2](#).

In our protocol we also listed the following issues that could be relevant:

- differences between studies with moderate and low risks of bias versus studies with high risks of bias: there were no studies considered to have a high risk of bias;
- assessment of publication bias: we did not investigate this with a funnel plot, because there were fewer than 10 studies;
- for patients with SD the reduction in medical costs was stronger after using the outcome of one study ([Smith 1986](#)) with imputing the standard error from another study ([Rost 1994](#)). For patients with SD the improvement in physical functioning disappeared after using the outcome of one study ([Smith 1986](#)), with imputing the pooled standard error from two other studies ([Rost 1994](#); [Dickinson 2003](#)).

Heterogeneity

We found no statistical indications for possible substantial heterogeneity and therefore undertook no decisions relevant to this.

DISCUSSION

Summary of main results

CL intervention

With regard to the CL intervention, the primary outcomes in the four studies showed a reduction in medical costs (three studies reported on this outcome). The reduction was greater for patients with SD ([Smith 1986](#); [Rost 1994](#)) than for patients with ASD ([Smith 1995](#)): in percentages these were reductions in median costs of 53%, 45% and 32.9% (costs for psychiatric care excluded). The reductions were mainly due to smaller reductions in types of inpatient medical consumption, with one study reporting a clear reduction in hospital days for patients with a SD ([Smith 1986](#)). The secondary outcomes showed an improvement in physical functioning for the patients with a SD, ASD and MSD. One study ([Smith 1986](#)) reported that for patients with a SD there was a reduction of physical functioning, but these data could not be used for pooling because there were no reported standard deviations. With use of an imputed SE for the outcome of this study, the pooled data still showed an improvement in physical functioning,

but no longer an improvement in the subgroup of patients with SD. For mental, social functioning and perceived health there were non-significant differences. There was a small reduction in perceived health. There were no data on sick leave or return to work.

Joint consultation and CL

Two studies reported on the intervention the joint consultation followed by a CL. In patients with somatoform disorders ([Van der Feltz 2006](#)) there were significant improvements in severity of somatization symptoms, medical consumption and social functioning. In the group of distressed high utilizers ([Katon 1992](#)), in which 73% fulfilled the criteria for ASD, there were no indications of effect of the intervention. In the intervention group in this study there were significant improvements in the use of antidepressants, the long-term use of antidepressants, and the antidepressant prescription rate among the physicians.

In conclusion, there is evidence that the use of a CL in primary care, in the treatment of patients with multiple MUPS, results in reduced medical costs (for SD and ASD) and improved physical functioning (for SD, ASD, MSD) with the strongest effects on SD, which is the most severe but also most rare disorder, regarding medical costs.

There is limited evidence that the use of a CL letter in primary care results in reduced inpatient medical consumption in patients with somatoform disorders

There is limited evidence that in primary care joint consultation with the patient with multiple MUPS by a psychiatrist, in the presence of the primary care physician, results in reduced symptom severity, reduced medical consumption and improved social functioning in patients with somatoform disorders

Overall completeness and applicability of evidence

Limitations

Some remarks should be made about the limitations in external validity:

Clinical relevance

First of all, two of the six studies ([Smith 1986](#); [Rost 1994](#)) concerned patients with a SD. This disorder is rare in primary care, with a prevalence of approximately 0.5% ([De Waal 2004](#)). This is in contrast to sub-threshold somatoform disorders, with a prevalence of 10-24% ([Escobar 1998](#); [Kroenke 2002](#); [De Waal 2004](#)). Therefore more weight should be given to the results in the patient groups with sub-threshold forms, showing less reduction in medical costs and less improvement of physical functioning than the patient groups with somatization disorder.

Health care setting, period

Five of the six studies were performed in the United States (the other study was performed in the Netherlands), so the results in other countries could vary considerably, due to differences in the role of the primary care physician and the insurance policies.

The outcomes which are reported in the studies vary. Concerning the main pathology, two studies reported on the severity of somatization symptoms and psychiatric comorbidity. The other four studies focused on SD, ASD and MSD, for which a lifetime history or a two-year history of MUPS and a symptom count is sufficient.

None of the studies were performed in an occupational health setting and there were no data on sub-populations of employees, so no conclusions can be drawn on the effect of the intervention for employees regarding return to work or functioning at work. The results show an effect on improving physical functioning and a small effect on reducing social function, which can be of importance in the functioning and return to work of employees, but no conclusions can be drawn with regard to the exact effects.

Furthermore, it should be borne in mind that four of the six included studies were from 1995 and earlier. The results of these studies are well known to many medical professionals, and health care has changed a lot since then. For example, the average duration of hospital admissions is greatly reduced. These are two reasons why these interventions will probably no longer achieve the same effect sizes.

Physician- versus patient-centred aspects

The interventions described in these studies are mainly physician-centred interventions. Only [Van der Feltz 2006](#) included a letter for the patient. Furthermore, four of the six studies did not measure patient-centred outcomes like symptom severity as primary outcomes or patient satisfaction as a secondary outcome. So this gives little insight as to how the patient-centred aspects of these interventions could be improved. In the light of the perceived reduced general health status of patients with persisting MUPS, this leaves room for further improvement.

Components of the intervention

There are three important aspects of interventions for patients with multiple and recurrent somatization symptoms: psychiatric screening, case management (e.g. regular appointments, and limiting referrals and diagnostic procedures) and patient-physician communication (e.g. take the patient seriously, don't tell the patient "it's all in your head", make a physical examination). From the results of our review it is not possible to draw any conclusions with regard to which aspects contributed most to the favourable outcomes. Further research is needed, but in the meantime attention must be paid to all three aspects.

Strengths

Strengths of the included studies, with regard to external validity, were that the study patients were of all ages, except children, and with a gender distribution comparable to what is reported in other studies concerning somatoform disorders. All the studies were performed in primary care, and urban and rural populations were involved. Although the results in patients with a SD were greater than in the patients with less serious somatization syndromes, the resulting reductions in medical costs and improvements in physical functioning were still significant. Given the high prevalence of sub-threshold somatization syndromes, there is a high potential for improvement in these outcomes in primary care.

Quality of the evidence

We assessed only one study as being of overall high quality ([Van der Feltz 2006](#)) (although see below for details of possible selection bias) and five studies as only of moderate quality with regard to internal validity. The conclusions mentioned above were, with regard to the CL intervention, drawn from four studies with 267 patients in the intervention condition (with 183 patients with ASD from [Dickinson 2003](#): lower totals for the 111 patients with MSD, and 88 patients with SD). With regard to the reduction in medical costs and improvement in physical functioning, these conclusions are to be interpreted with caution, due to the fact that these results are established in diagnostic subgroups and lack transparency in the underlying studies. Furthermore, the results are varying, with one study in patients with a SD ([Smith 1986a](#)) reporting a negative effect on physical functioning, although this was in a small study population, and if the results could have been pooled the results would still have been positive.

The conclusions regarding joint consultation of the psychiatrist in the presence of the primary care physician, followed by a CL, concerned two studies with 182 patients in the intervention condition. The patient populations were quite different. The patients in the study of distressed high utilizers did not all fulfil the inclusion criteria, and there was no subgroup analysis on the patients who fulfilled the criteria for ASD (73%) and for SD (20.2%). In the last group there was selection bias, due to the fact that the included patients were selected because they were highly distressed, whereas not all patients with somatoform disorders are distressed. Therefore conclusions with regard to the effect of consultation with the psychiatrist, with the use of a CL can only be drawn from the results of the study with patients with somatoform disorders ([Van der Feltz 2006](#)), providing limited evidence.

One study ([Dickinson 2003](#)) showed an important overlap between the patients with SD, ASD and MSD. A study of patients fulfilling only the criteria for MSD and not SD and ASD would have given a clearer indication of the effect of the intervention on patients with this less serious form of somatoform disorders.

Due to the study design, one study with cluster randomization ([Van der Feltz 2006](#)) had a small control group. Although we as-

sessed this study of high quality, it should be taken into account that selection bias could have been of influence, which should be kept in mind when interpreting the results. In this study there was heterogeneity of the included patients; for example 34% of the patients fulfilled the criteria for undifferentiated somatoform disorder, 25% for persistent pain disorder and 15% for hypochondriasis. A strong point is that this heterogeneity reflects the patient population in primary care.

All studies were of moderate and high quality, and therefore no analysis was done for the included studies to control for the inclusion of low quality studies.

Potential biases in the review process

For the inclusion of the studies we chose a definition with high sensitivity and low specificity. The relatively low number of included studies indicates that this was probably a good approach. The intervention consisted of two components (psychiatric screening and a CL) which we defined in different ways for our search. It is possible that we missed studies which defined one or two components in other terms.

One can also argue that our perspective was too narrow. In the field of consultation-liaison psychiatry, interventions with psychiatric screening and the use of a CL have evolved to collaborative care with, amongst other things, the involvement of mental health specialists and education of the patient. Although this is a promising development, these are complex interventions to assess in patients with a broad scale of psychiatric disorders. We chose an intervention with two components and the patient group with MUPS to obtain insight into the critical components of the effect.

However, one question in our review remains: is there a critical element in the two components of screening for the diagnosis and the guidelines for treatment? Does the uncertainty of the diagnosis hamper the primary care physician providing care for patients with MUPS? Or does the primary care physician not apply the recommendations adequately without the 'reminder' of a CL? To our knowledge there are no studies which the two components have been evaluated separately.

We used the Cochrane Collaboration's Risk of Bias Tool (Higgins 2008a), adding three additional criteria because of the complicated assessment of patients with MUPS, the role of comorbidity and the potential pre-randomization bias. While we were completing this review, guidelines for assessing the quality of RCTs were updated. Using the GRADE approach would have resulted in a more qualified description of the strength of evidence, and we recommend using this approach in future revisions. However, we think that we checked the main factors determining the quality of the RCTs (Feinstein 1985) and that we detected most risks of bias. The impossibility of blinding of care providers stays associated with these kind of interventions, and in analogy blinding can not be avoided for patients in joint consultations.

Agreements and disagreements with other studies or reviews

To our knowledge this is the first review on the effectiveness of CLs. Most reviews on the treatment of patients with MUPS focus on the effectiveness of cognitive behavioural therapy (CBT) and antidepressants. A small number of reviews involved the topic of CLs.

The results of our review are in line with the findings of Looper and Kirmayer (Looper 2002) in their review of behavioral approaches to somatoform disorders and the review on the effectiveness of treatments for somatization in general practice in Blankenstein's thesis (Blankenstein 2001). They reviewed the same studies as we did (until 2002), although Looper did not include the Katon study of distressed high utilizers. We found more evidence than Sumathipala 2007, who stated that there was limited evidence for the effectiveness of CLs for patients with MUPS in terms of reducing medical health charges and improving physical functioning. He referred to Rost 1994 and Smith 1995. If our findings are broadened, they are also in line with the findings of Henningsen 2007, who performed a review on the management of functional somatic syndromes (FSS). Earlier research indicates that there is much overlap in symptoms between the different somatic syndromes and somatoform disorders (Wessely 1999). Although Henningsen 2007 had no specific focus on CLs, they stated that the therapeutic rationale of the effect of non-pharmacological treatments (psychotherapy and graded exercise) in FSS is that these treatments typically aim at overall function and not the alleviation of specific symptoms. In this rationale there is overlap with how the intervention of CL might work in patients with MUPS, whereas the CL is more aimed at handling the consequences of MUPS than the causes.

Three reviews show that CBT and antidepressants are the most effective treatment options for patients with multiple MUPS (Kroenke 2000; Looper 2002; Sumathipala 2007). However, interpretation of this evidence should take into account that patients with multiple MUPS vary in their willingness to be referred to a mental health specialist. In most of the RCTs used for the reviews there was acceptable compliance, defined in one review as two-thirds (Looper 2002), but pre-randomization dropout was seldom described adequately. Furthermore, it is important to remember that the results of this review are based on five of six studies performed in United States healthcare settings. Outcomes could vary in other countries with different healthcare settings and, for example, more or fewer possibilities at point of use to the consumer. Applying the recommendations of CLs does not mean that the patients will be less worried or more satisfied with care. Indeed our results show that there is a slight reduction in perceived and general health. The primary care physician should take this into account and also address the worries of the patient. How to give good reassurance is still a topic of further investigations, but recent studies (Epstein 2007; Salmon 2007) have reported that when physicians reacted on the concerns of patients with MUPS with

empathy, this resulted in more satisfaction with the patient-physician relationship.

No direct evidence is available to make it possible to draw conclusions on the best care for employees with MUPS, in relation to their functioning at work and return to work from sick absence. However, from the evidence obtained from primary care, it can be concluded indirectly that the diagnosis of MUPS and adherence to the guidelines will contribute to an improvement in at least physical functioning. Since interventions result in a reduction in hospital stays and 'bed days' it is possible that applying these interventions to employees with MUPS in occupational health care will lead to a reduction in the period and/or frequency of sickness absence.

AUTHORS' CONCLUSIONS

Implications for practice

- There is evidence from studies of moderate quality that the use of CLs in primary care is effective, but primarily with regard to healthcare (provider) related outcomes, in reducing financial costs, and only secondary for patient-related outcomes, in improving physical functioning.
- There is evidence from studies of moderate quality that if primary care physicians are taught to take patients with persistent MUPS seriously, see these patients at regular intervals, and perform physical examinations at each visit, but do not make referrals or further investigation unless there is a clear indication, that this will result in fewer medical costs, less medical consumption (especially hospital days) and better physical functioning.
- There is limited evidence that joint consultation with the patient (by the psychiatrist in the presence of the physician) results in a reduction of severity of somatization symptoms, less medical consumption and improved social functioning.
- Other interventions are needed when psychiatric comorbidity, mental functioning, social functioning and disability are (also) to be addressed in patients with somatization symptoms.
- Other health care professionals should be careful with referrals and diagnostic procedures for patients with somatization

symptoms, and should first communicate with the primary care physician. Furthermore, in caring for these patients, attention should be paid to the management of communication (as mentioned in the CL).

Implications for research

Further RCTs and studies are needed to address the following issues:

- To evaluate both the CL intervention and the CL intervention with joint consultation with the patient, with emphasis on the severity of somatization symptoms, psychiatric comorbidity, functioning and patient satisfaction as outcomes.
- To assess pre-randomization dropout rates.
- To clarify how a diagnosis of somatoform disorders or MUPS helps in the therapeutic choices and communication in care, and what the critical components are in the recommendations, with regard to aspects of case management and communication, preferably by means of qualitative research and testing tailored interventions in RCTs.
- To tailor the intervention more to the patient's or physicians's perspective, preferably by means of qualitative research and testing tailored interventions in RCTs.
- To evaluate these interventions in countries with other healthcare systems than the United States.
- To evaluate these interventions in the field of occupational health, with physical, mental and social functioning, return to work, frequency and duration of sickness absence of employees as primary outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dickinson 2003

Methods	RCT to compare two conditions. Randomization at patient level. Assessments on three occasions: baseline, 6 and 12 months after enrolment. After 1 year single cross-over for the patients in the control condition
Participants	188 patients with somatoform symptoms, from 3 primary care clinics, who were reclassified into three groups, meeting criteria for 1) somatization disorder (SD; n = 88, mean age 46.9 years, standard deviation 15.9 years) 2) abridged somatization disorder (ASD; n = 183, mean age 47.5 years, standard deviation 14.9 years) 3) multisomatoform disorder (MSD; n = 111, mean age 46.6 years, standard deviation 15.3 years)
Interventions	a) Screening: by an interviewer who used an 11-item screening for unexplained physical symptoms. For all patients with 3 or more positive items on the screening, a diagnostic interview was performed by a trained interviewer, using the somatization section of the NIMH Diagnostic Interview Schedule (DIS) Version III-R. The results were reviewed by the study physician to confirm that the physical symptoms were medically unexplained. Patients were selected if they fulfilled the criteria for SD, ASD or MSD. b) Intervention: the family physicians of patients of the intervention group were sent a Care Recommendation letter about the patients who met the criteria for a somatoform disorder. This letter consisted of the components mentioned in the Notes of Smith 1986 .
Outcomes	1 year follow-up: intervention (I) superior to control (C) on physical functioning (SF-36: PCS) in all 3 groups. No differences in mental functioning (SF-36: MCS) in all 3 groups
Notes	Lost to follow-up 37/188 (no specification I or C and SD, ASD or MSD) Study location: Mobile, Alabama, USA. Study period: 1992-1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Only the randomization is mentioned, not the method by which it is performed
Allocation concealment?	Unclear risk	Not mentioned in the study text
Blinding? Blinding of patients?	Low risk	For patients and outcome assessors, not for providers of care due to type of intervention

Incomplete outcome data addressed? All outcomes	Unclear risk	No significant differences on baseline characteristics for responders and non-responders. 19.5% and 39.5% non-responders at 12 and 24 months respectively, with no report on distribution over I and C group. No imputation for loss to follow-up reported
Free of selective reporting?	Low risk	Expected outcomes present; only physical and mental functioning were measured, but this was intended
Free of other bias?	Low risk	Cross-over design, but complete data I and C for first and second phase, which enabled assessment of carry-on effects
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, age, sex and socio-economic status
Were MUPS assessed with validated instruments?	Low risk	Clinical interviewer applying the DIS (DSM-III-R-version).
Was there an acceptable pre-randomisation dropout?	Low risk	Patients were first screened by primary care physicians (from top 10% ambulatory healthcare visits from registrations) and after that by a research team. From the patients fulfilling the screening criteria, 6.7% refused to be randomized, in total 14% did not participate in randomization, due to inability to contact and other difficulties. Characteristics of refusers not described

Katon 1992

Methods	RCT to compare two conditions. Randomization stratified at physician level. Assessment on three occasions: baseline, 6 and 12 months.
Participants	Total 251 patients, I: 124 patients C: 127 patients (mean age I 45.1 years, SD 12.6 years, and C 48.9 years, SD 14.1 years) from 2 primary care clinics whose health care utilization placed them in the top 10% and who met any of three screen criteria for psychiatric distress. 20.2% fulfilled the criteria for SD
Interventions	a) Screening on 3 criteria: 1) Sum of SCL item scores for anxiety and depression scores greater than 13 2) Sum of SCL somatization score greater than 9. 3) Referral from the primary care physician for psychiatric consultation Patients who met any of the three screening criteria were interviewed for 1 hour by a study psychiatrist using the NIMH DIS version 3 A. b) Intervention: The patient was interviewed for half an hour by the study psychiatrist

Katon 1992 (Continued)

	with the primary care physician present. The primary care physician was provided with a written psychiatric CL, a brief written protocol for recommended treatment and an article on treatment of the specific mental disorder. During the course of the study the study psychiatrist had one meeting with the participating physician to review the management of the patient	
Outcomes	1 year follow-up: I no significant differences compared to C with regard to medical consumption, somatization, mental health or disability, except in I higher prescription rate for antidepressant medication and higher sustained use by patients, compared to C	
Notes	Lost to follow-up 18/251 (I: 9/124, C: 9/127). Study location: Western Washington State Arkansas, USA. Study period: Not specified, before 1992.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Stratified by physician.
Allocation concealment?	Unclear risk	Only short description of the randomization, no details about allocation concealment
Blinding? Blinding of patients?	High risk	Due to type of intervention physicians and patients not blinded, outcome assessors were blinded
Incomplete outcome data addressed? All outcomes	Unclear risk	No imputation for loss to follow-up reported.
Free of selective reporting?	Unclear risk	Expected outcomes present, but not specified for patients with somatoform disorders without explicit reasons for this
Free of other bias?	Low risk	No indications of other bias found
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, age, sex and socio-economic status
Were MUPS assessed with validated instruments?	Low risk	By psychiatrist and SCL-90 questionnaire.
Was there an acceptable pre-randomisation dropout?	High risk	26% of the selected patients did not participate in randomization. Reasons were not mentioned. Refusers were less depressed and disabled than participants

Rost 1994

Methods	RCT to compare two conditions. Randomization at physician level. Assessment on 4 occasions: baseline, 4, 8 and 12 months
Participants	73 patients I: 40 patients, C: 33 patients (mean age I 44.6 years, standard deviation 8.5 years, and C 43.4 years, SD 10.0 years) from primary care practices fulfilling the criteria for SD. Care provided by 59 primary care physicians
Interventions	a) Screening: by means of a semi-structured interview with the research assistant and a checklist with DSM-III-R criteria for SD. The research psychiatrist determined the number of unexplained medical symptoms. b) Intervention: the physicians in the I-group received a CL (see Notes Smith 1986).
Outcomes	1 year follow-up: I superior to C on medical costs (US Dollars) and physical functioning (Rand physical health). No significant differences in mental functioning (Rand mental health)
Notes	Lost to follow-up 3/73 (no specification I or C). Study location: Central Arkansas, USA. Study period: not specified (before 1995, all costs reattributed to 1990 dollars)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Only the randomization is mentioned, not the method by which it is performed
Allocation concealment?	Unclear risk	No details about allocation concealment reported
Blinding? Blinding of patients?	Low risk	For patients and outcome assessors, not for providers of care due to type of intervention
Incomplete outcome data addressed? All outcomes	Unclear risk	No imputation for loss for follow-up reported.
Free of selective reporting?	Low risk	Expected outcomes are presented
Free of other bias?	Low risk	Cross-over design, but complete data for I and C for first and second phase, which enables assessing carry-on effects
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, age, sex and education.
Were MUPS assessed with validated instruments?	Low risk	By psychiatrist.

Rost 1994 (Continued)

Was there an acceptable pre-randomisation dropout?	Low risk	After selection by primary care physicians, all selected patients who met the study criteria participated in randomization
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Smith 1986

Methods	RCT to compare two conditions. Randomization at physician level. Assessment on 2 occasions: baseline, 9 months. After 9 months single cross over for the control condition	
Participants	38 patients I: 19 patients, C: 19 patients (mean age I 45 years, standard deviation 11.5 years, and C 44.8 years SD 13.9 years) from private and university family practices, fulfilling the criteria for SD. Care provided by 35 primary care physicians	
Interventions	<p>The CL described the diagnosis of SD, its chronic relapsing course, and its low mortality and morbidity rates. It also contained recommendations for management and suggested that:</p> <ul style="list-style-type: none"> - Regular appointments should be made for the patient (possibly every 4 to 6 weeks) - Physical examinations should be performed at each visit, so that the symptoms would not be taken at face value - Physicians should avoid hospitalization of the patient, diagnostic procedures, surgery and the use of laboratory assessments unless they were clearly indicated - Physicians were encouraged not to tell patients "it's all in your head" 	
Outcomes	9 months follow-up: I superior to C on medical costs (US dollars) and medical consumption (annual hospital days). No significant differences in physical or mental health (Rand physical and mental health)	
Notes	<p>Lost to follow-up 3/41 (no specification I or C).</p> <p>Study location: Central Arkansas, USA.</p> <p>Study period: 1980-1983.</p>	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Assignment on physician level.
Allocation concealment?	Low risk	With a sequential log.
Blinding? Blinding of patients?	Low risk	For patients and outcome assessors, not for providers of care due to type of intervention
Incomplete outcome data addressed? All outcomes	Unclear risk	No imputation for loss for follow-up reported.
Free of selective reporting?	Low risk	Expected outcomes are presented

Smith 1986 (Continued)

Free of other bias?	Low risk	Cross-over design, but complete data for I and C for first and second phase, which enables assessing carry-on effects
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, sex, age and socio-economic class.
Were MUPS assessed with validated instruments?	Low risk	By psychiatrist.
Was there an acceptable pre-randomisation dropout?	Low risk	After selection by primary care physicians, 7.3% of the selected patients who met the study criteria refused participation in randomization

Smith 1995

Methods	RCT to compare two conditions. Randomization at physician level. Assessment on 4 occasions: baseline, 4 months, 8 months and 1 year. After 1 year single cross over for the control condition	
Participants	56 patients I: 27 patients (mean age 42.2 years, standard deviation 12.3 years) C: 29 patients (mean age 43.9 years, standard deviation 12.5 years) from private and university family practices. Care provided by 51 primary care physicians	
Interventions	a) Screening: a semi-structured interview with the research assistant and a checklist with DSM-III-R criteria for SD. The research psychiatrist determined the number of unexplained medical symptoms. b) Intervention: the physicians in the I group received a CL (see Notes Smith 1986).	
Outcomes	1 year follow up: I superior to C on medical costs (US dollars) and physical functioning (Rand physical health). No significant differences in hospital days, outpatient visits or mental health	
Notes	Lost to follow-up 2/56 (no specification I or C).	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Only the randomization is mentioned, not the method by which it is performed
Allocation concealment?	Unclear risk	Not mentioned in the study text
Blinding? Blinding of patients?	Low risk	For patients and outcome assessors, not for providers of care due to type of intervention

Smith 1995 (Continued)

Incomplete outcome data addressed? All outcomes	Low risk	No subject was missing data for more than two follow-up periods
Free of selective reporting?	Low risk	Expected outcomes present.
Free of other bias?	Low risk	Cross-over design, but complete data for I and C for first and second phase, which enables assessing carry-on effects
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, age, sex and education.
Were MUPS assessed with validated instruments?	Low risk	By psychiatrist.
Was there an acceptable pre-randomisation dropout?	Low risk	After selection by primary care physicians, all selected patients who met the study criteria participated in randomization

Van der Feltz 2006

Methods	RCT to compare two conditions. Randomization at practice level. Assessment on 3 occasions: baseline, 6 weeks and 6 months.
Participants	81 patients (mean age 44, range 20-77 years) I: 58 patients C: 23 patients. Patients were receiving care in 36 primary care practices
Interventions	a) Screening: by general practitioners who selected patients who fulfilled two criteria: 1) previous referral for symptoms that remain unexplained after specialist diagnostic examination 2) continuing requests from the patient for further diagnostic procedures. These patients completed a baseline questionnaire checking ICD-10 criteria for main categories of somatoform disorders and the Whitely Index. b) Intervention: The GPs in I and C were given training in case-management, reattribution and cognitive behavioural techniques in 3 to 9 three hours sessions. The patients had a one-hour interview with the psychiatrist in the presence of the primary care physician. The psychiatrist summarized the diagnosis, reattribution and specific treatment advice in a CL for both the primary care physician and the patient
Outcomes	6-months follow-up: I superior to C on health care utilization (VDHCP), severity of main explained medical symptoms (Speckens checklist) and social interaction (SIP)
Notes	Lost to follow-up 0/81. Study location: Amsterdam, The Netherlands. Study period: 1999-2001 (personal communication authors).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization on practice level.
Allocation concealment?	Low risk	GPs and patients blinded about the treatment allocation
Blinding? Blinding of patients?	High risk	Due to type of intervention physicians and patients not blinded, outcome assessors were blinded
Incomplete outcome data addressed? All outcomes	Low risk	Data complete at follow-up, no non-responders at follow-up.
Free of selective reporting?	Low risk	Expected outcomes are presented
Free of other bias?	High risk	18 practices provided 58 patients for the I condition and 18 practices 23 patients for the C condition because physicians were no longer blinded for the condition, thereby potentially enhancing selection bias
Complete description of baseline characteristics?	Low risk	Psychiatric co-morbidity, sex, age and socio-economic status
Were MUPS assessed with validated instruments?	Low risk	By psychiatrist and SCL-90 questionnaire.
Was there an acceptable pre-randomisation dropout?	Low risk	After screening by primary care physicians, from the eligible patients 12% refused participation in randomization. Refusers did not differ from participants in demographic and clinical characteristics

ASD: abridged somatization disorder

C: control

CL: consultation letter

DIS: diagnostic interview schedule

I: intervention

MSD: multisomatoform disorder

NIMH: National Institute of Mental Health

RCT: randomized controlled trial

SD: somatization disorder

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allen 2006	The 'isolated' effects of the CL could not be assessed because it was used in the intervention and the controlled condition
Barsky 2004	The 'isolated' effects of the CL could not be assessed because it was used in the intervention and the controlled condition The patients were selected on criteria for hypochondriasis and not for somatization
Carr 1997	Not an RCT. Case-control design.
De Cruppe 2005	The population was from secondary care and the primary care physician was not the most important caregiver
Escobar 2007	The 'isolated' effects of the CL could not be assessed because it was used in the intervention and the controlled condition
Koopmans 1996	The population was from secondary care and the primary care physician was not the most important caregiver
Liu 2007	Outcome for somatization not measured.
Meeuwesen 1994	The population was from secondary care and the primary care physician was not the most important caregiver

DATA AND ANALYSES

Comparison 1. Consultation letter versus CAU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outpatient medical consumption: outpatient visits	1		Mean Difference (Fixed, 95% CI)	0.20 [-0.38, 0.78]
1.1 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	0.20 [-0.38, 0.78]
2 Inpatient medical consumption: emergency department visits	1		Mean Difference (Fixed, 95% CI)	-0.7 [-2.72, 1.32]
2.1 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-0.7 [-2.72, 1.32]
3 Inpatient medical consumption: hospital days	1		Mean Difference (Fixed, 95% CI)	-0.5 [-6.96, 5.96]
3.1 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-0.5 [-6.96, 5.96]
4 Medical costs	2		Mean Difference (Fixed, 95% CI)	-352.55 [-522.32, -182.78]
4.1 Somatization disorder	1		Mean Difference (Fixed, 95% CI)	-466.0 [-749.49, -182.51]
4.2 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-289.11 [-501.10, -77.12]
5 Physical functioning	3		Mean Difference (Fixed, 95% CI)	5.71 [4.10, 7.33]
5.1 Somatization disorder	2		Mean Difference (Fixed, 95% CI)	7.57 [4.04, 11.09]
5.2 Abridged somatization disorder	2		Mean Difference (Fixed, 95% CI)	5.07 [2.81, 7.33]
5.3 Multisomatoform disorder	1		Mean Difference (Fixed, 95% CI)	5.5 [2.45, 8.55]
6 Mental functioning	2		Mean Difference (Fixed, 95% CI)	-0.66 [-2.21, 0.90]
6.1 Somatization disorder	1		Mean Difference (Fixed, 95% CI)	5.0 [-5.30, 15.30]
6.2 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-0.79 [-2.37, 0.79]
7 Social functioning	2		Mean Difference (Fixed, 95% CI)	-0.99 [-2.64, 0.66]
7.1 Somatization disorder	1		Mean Difference (Fixed, 95% CI)	-1.7 [-12.55, 9.15]
7.2 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-0.97 [-2.64, 0.70]
8 Health perceptions	2		Mean Difference (Fixed, 95% CI)	-2.13 [-4.33, 0.08]
8.1 Somatization disorder	1		Mean Difference (Fixed, 95% CI)	-0.5 [-9.45, 8.45]
8.2 Abridged somatization disorder	1		Mean Difference (Fixed, 95% CI)	-2.23 [-4.50, 0.04]

Comparison 2. Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary care medical consumption	1		Mean Difference (Fixed, 95% CI)	-9.85 [-15.18, -4.52]
1.1 Somatoform disorders	1		Mean Difference (Fixed, 95% CI)	-9.85 [-15.18, -4.52]
2 Total healthcare medical consumption	1		Mean Difference (Fixed, 95% CI)	-95.97 [-148.71, -43.23]
2.1 Somatoform disorders	1		Mean Difference (Fixed, 95% CI)	-95.97 [-148.71, -43.23]
3 Somatization symptom severity	1		Mean Difference (Fixed, 95% CI)	-1.45 [-1.90, 1.00]
3.1 Somatoform disorders	1		Mean Difference (Fixed, 95% CI)	-1.45 [-1.90, 1.00]
4 Social functioning	1		Mean Difference (Fixed, 95% CI)	9.93 [1.48, 18.39]
4.1 Somatoform disorders	1		Mean Difference (Fixed, 95% CI)	9.93 [1.48, 18.39]

Comparison 3. Consultation letter versus CAU with study results imputed for SD

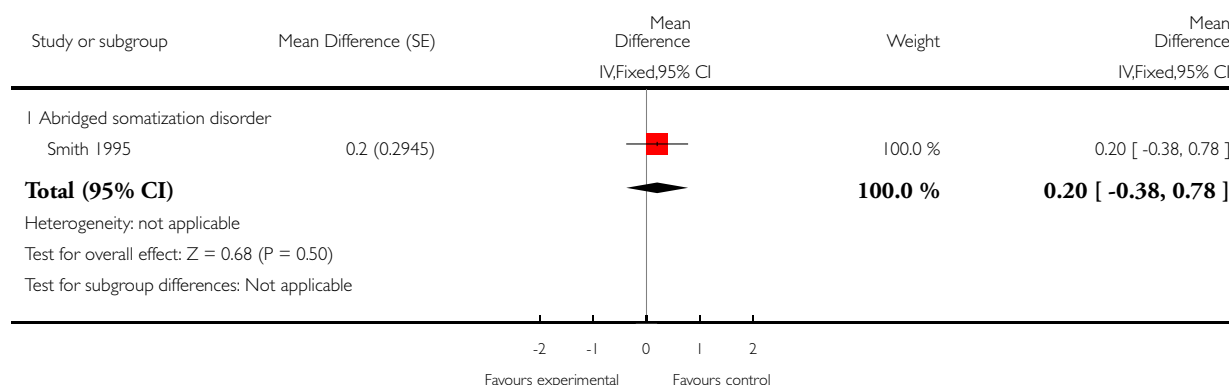
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Medical costs	3		Mean Difference (Fixed, 95% CI)	-422.36 [-568.01, -276.71]
1.1 Somatization disorder	2		Mean Difference (Fixed, 95% CI)	-541.5 [-741.96, -341.04]
1.2 Abridged somatisation disorder	1		Mean Difference (Fixed, 95% CI)	-289.11 [-501.10, -77.12]
2 Physical functioning	4		Mean Difference (Fixed, 95% CI)	3.57 [2.07, 5.07]
2.1 Somatization disorder	3		Mean Difference (Fixed, 95% CI)	0.02 [-2.64, 2.68]
2.2 Abridged somatization disorder	2		Mean Difference (Fixed, 95% CI)	5.07 [2.81, 7.33]
2.3 Multisomatoform disorder	1		Mean Difference (Fixed, 95% CI)	5.5 [2.45, 8.55]

Analysis 1.1. Comparison 1 Consultation letter versus CAU, Outcome 1 Outpatient medical consumption: outpatient visits.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 1 Outpatient medical consumption: outpatient visits

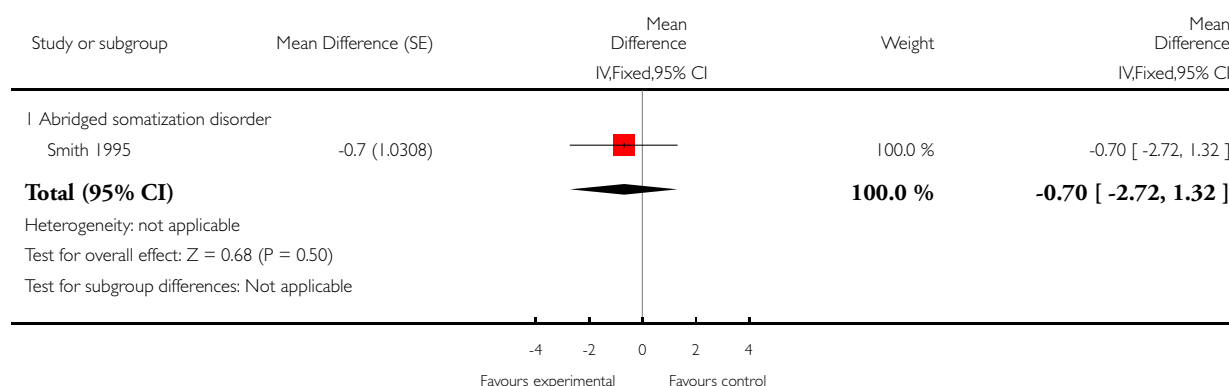


Analysis 1.2. Comparison 1 Consultation letter versus CAU, Outcome 2 Inpatient medical consumption: emergency department visits.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 2 Inpatient medical consumption: emergency department visits

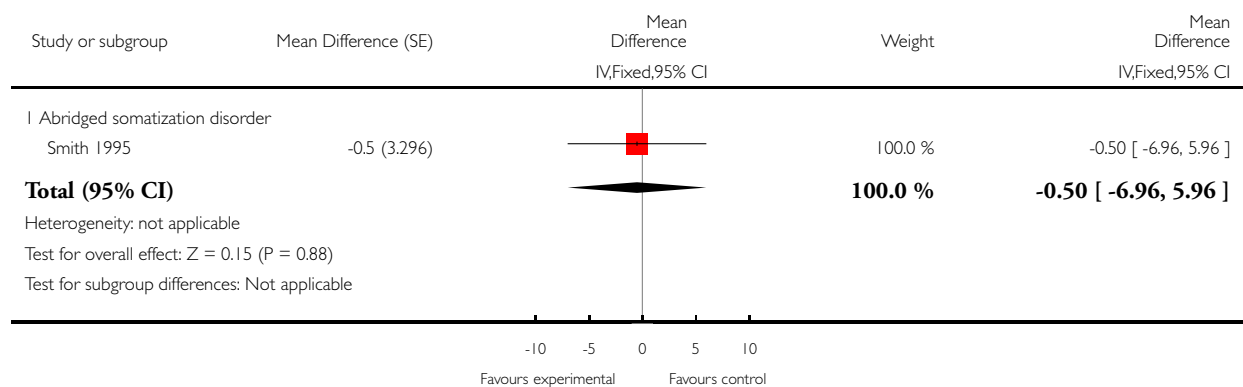


Analysis 1.3. Comparison 1 Consultation letter versus CAU, Outcome 3 Inpatient medical consumption: hospital days.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 3 Inpatient medical consumption: hospital days

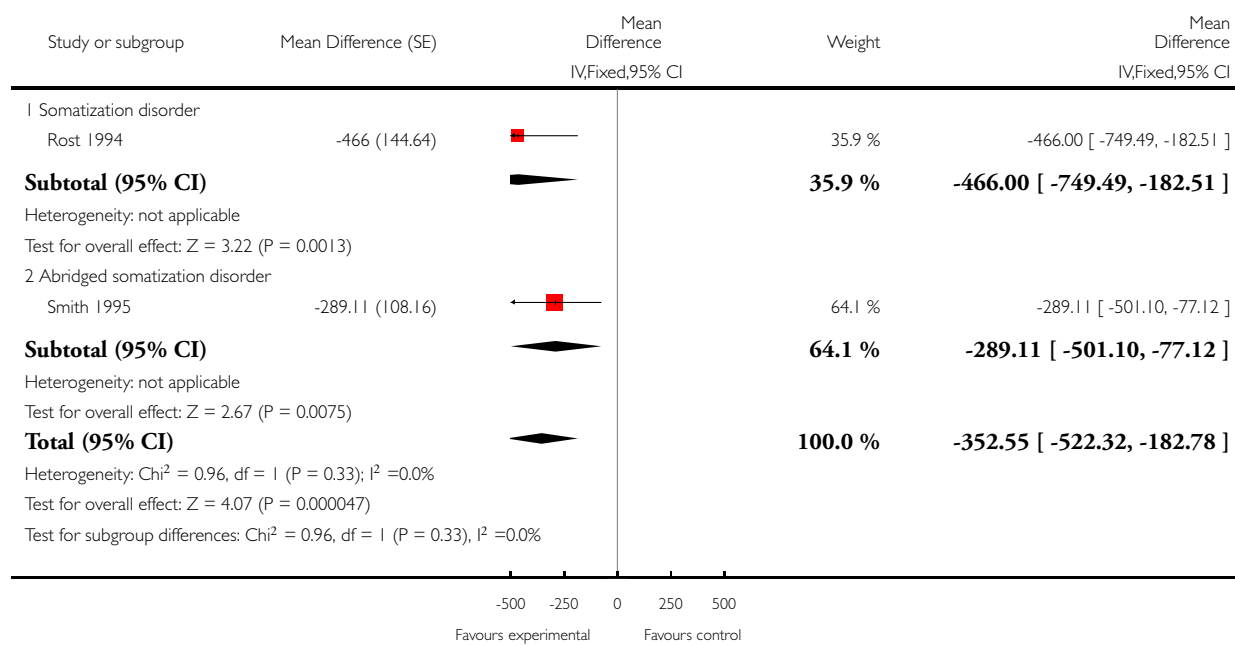


Analysis 1.4. Comparison 1 Consultation letter versus CAU, Outcome 4 Medical costs.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 4 Medical costs

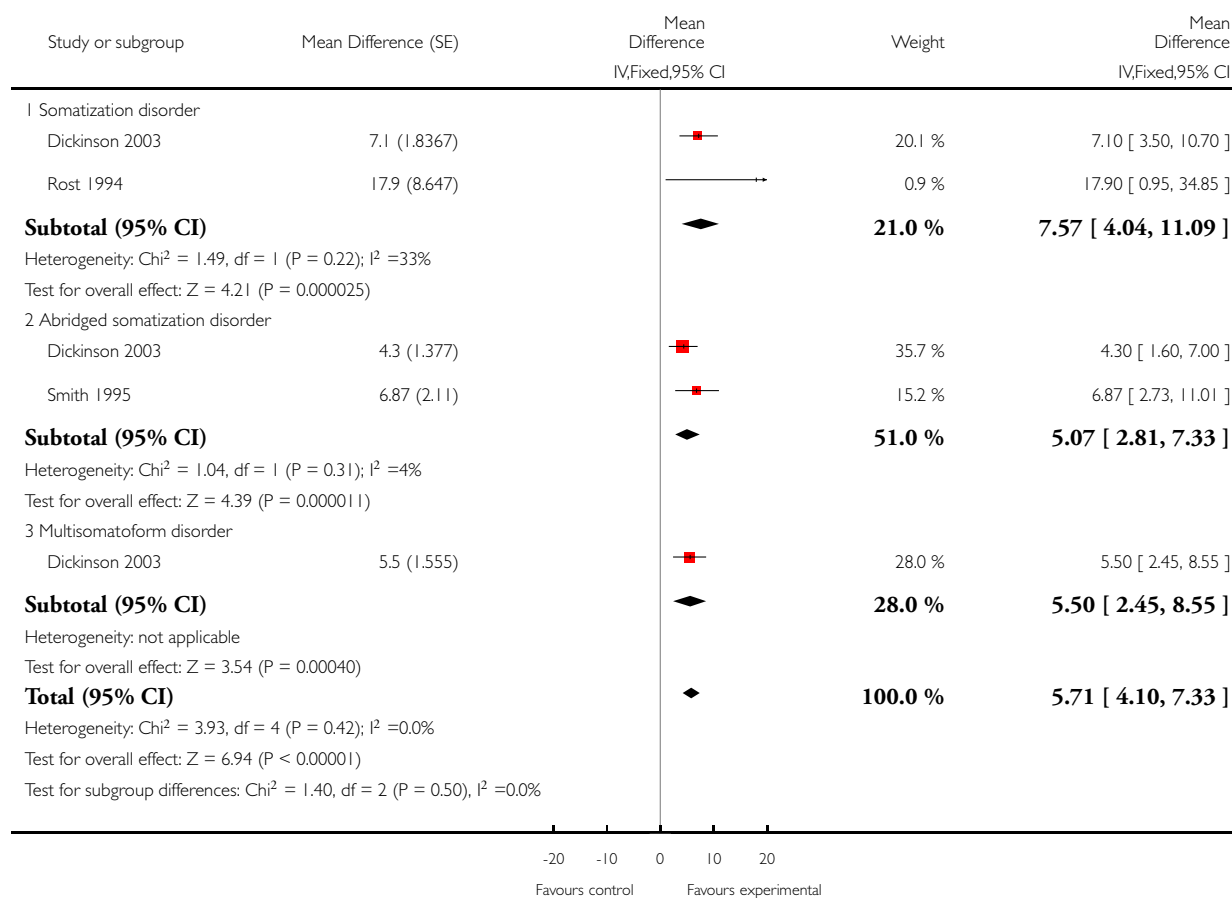


Analysis 1.5. Comparison 1 Consultation letter versus CAU, Outcome 5 Physical functioning.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 5 Physical functioning

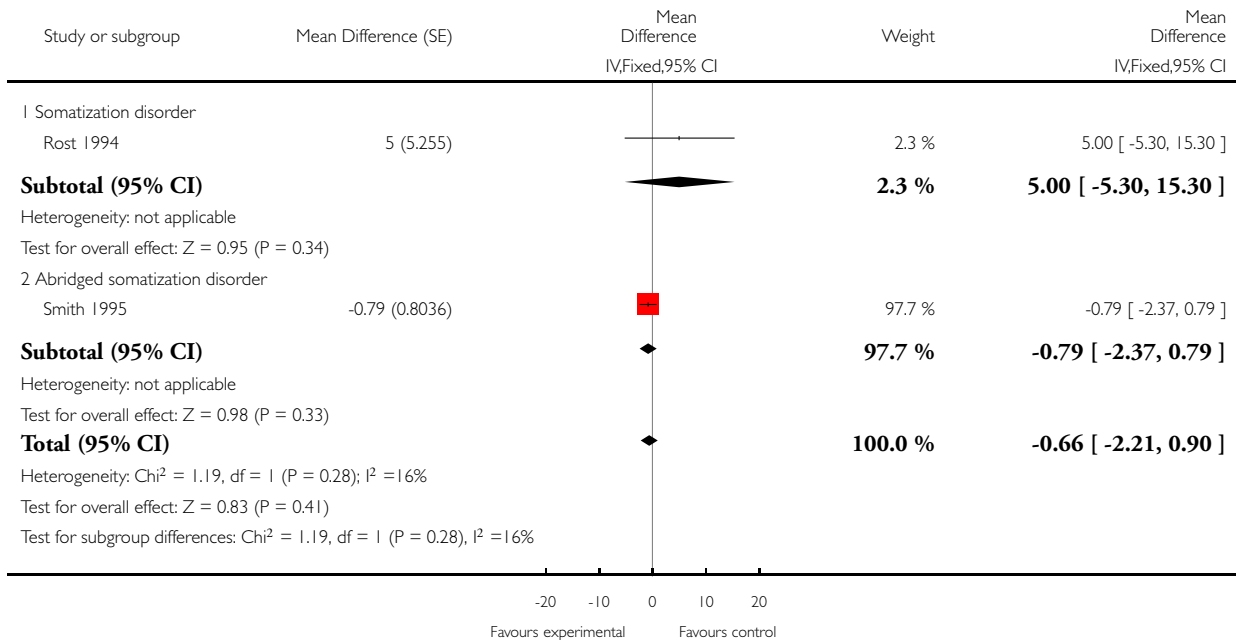


Analysis 1.6. Comparison 1 Consultation letter versus CAU, Outcome 6 Mental functioning.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 6 Mental functioning

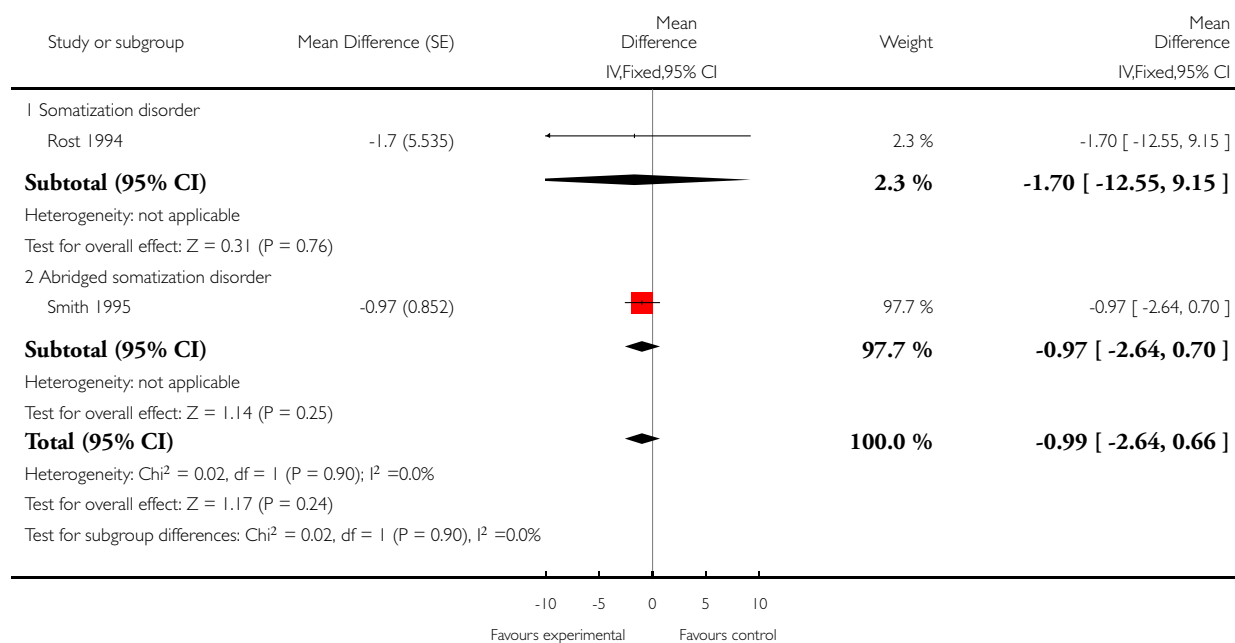


Analysis 1.7. Comparison 1 Consultation letter versus CAU, Outcome 7 Social functioning.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 7 Social functioning

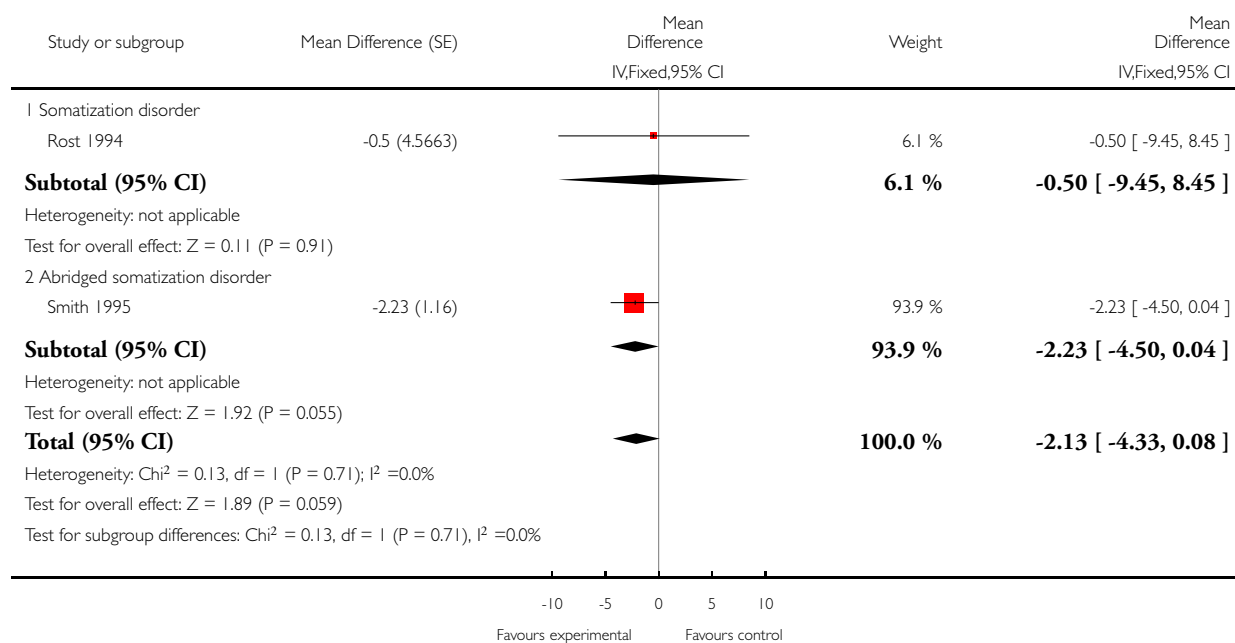


Analysis 1.8. Comparison 1 Consultation letter versus CAU, Outcome 8 Health perceptions.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 1 Consultation letter versus CAU

Outcome: 8 Health perceptions

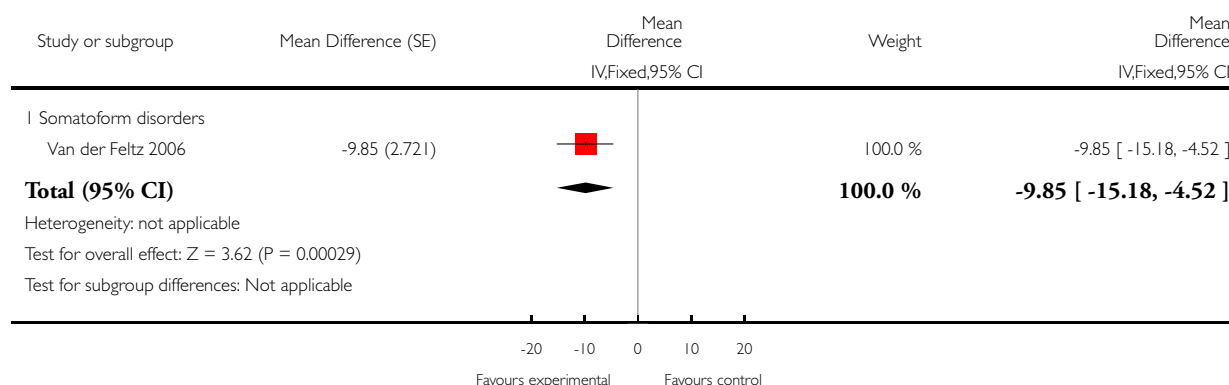


Analysis 2.1. Comparison 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual, Outcome 1 Primary care medical consumption.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual

Outcome: 1 Primary care medical consumption

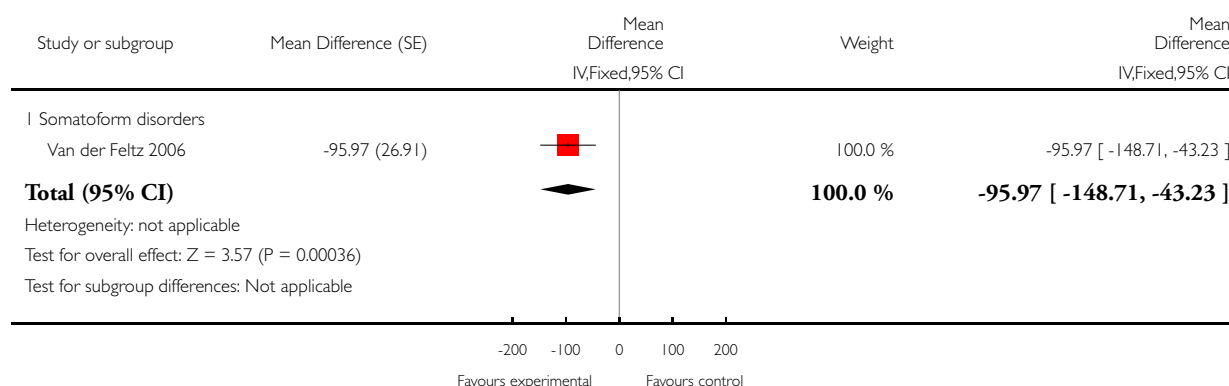


Analysis 2.2. Comparison 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual, Outcome 2 Total healthcare medical consumption.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual

Outcome: 2 Total healthcare medical consumption

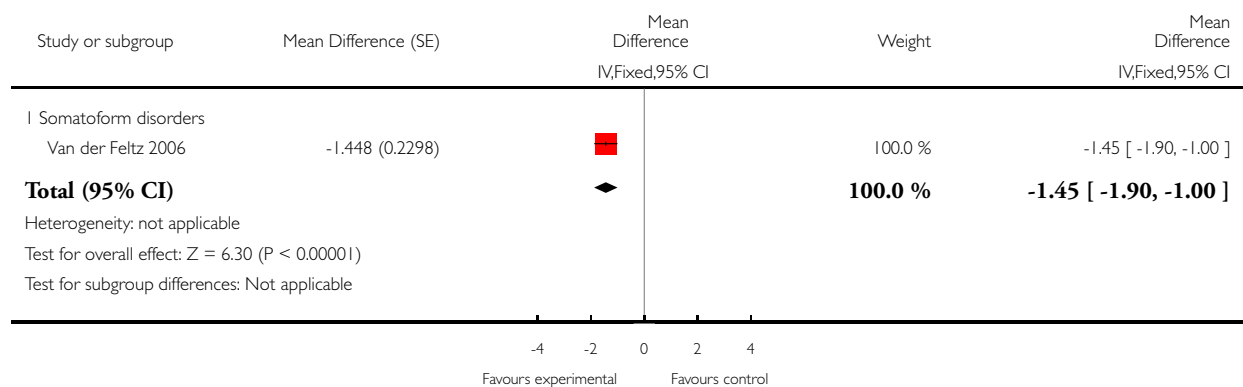


Analysis 2.3. Comparison 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual, Outcome 3 Somatization symptom severity.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual

Outcome: 3 Somatization symptom severity

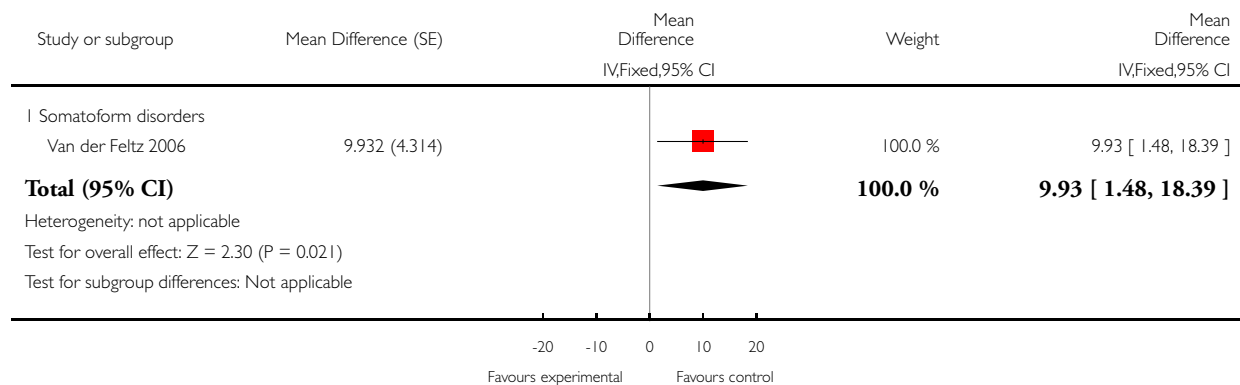


Analysis 2.4. Comparison 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual, Outcome 4 Social functioning.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 2 Consult of patient by psychiatrist with the physician present and consultation letter versus care as usual

Outcome: 4 Social functioning

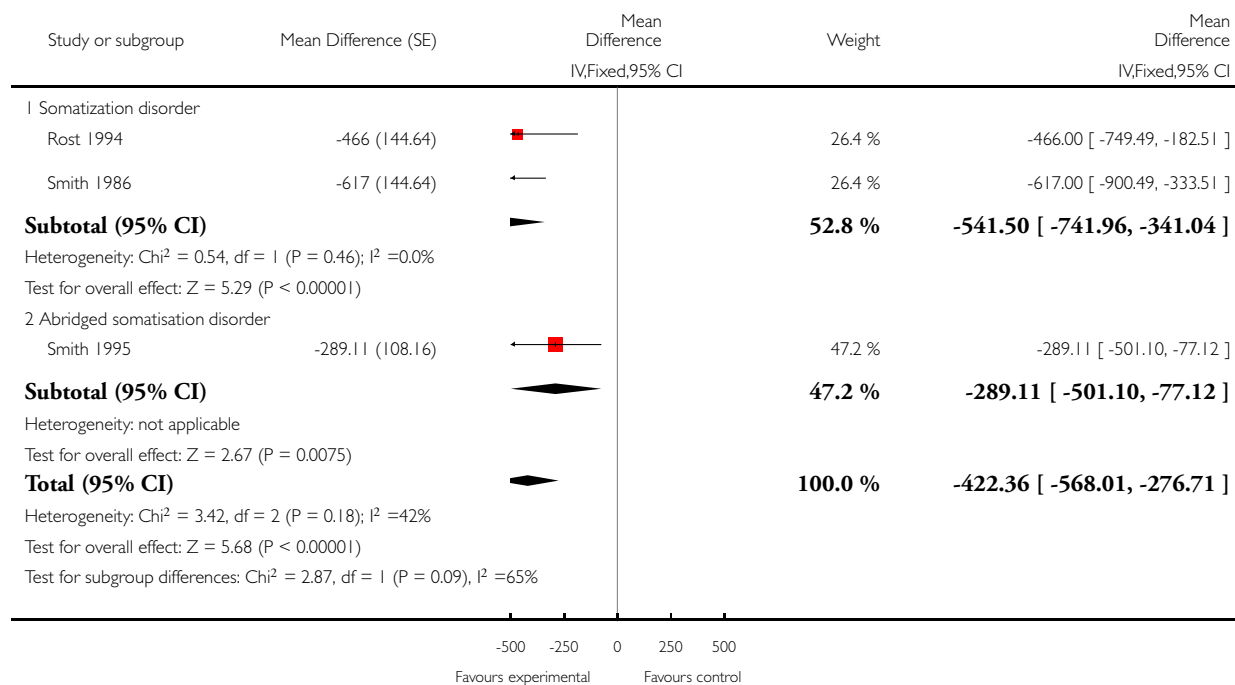


Analysis 3.1. Comparison 3 Consultation letter versus CAU with study results imputed for SD, Outcome 1 Medical costs.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 3 Consultation letter versus CAU with study results imputed for SD

Outcome: 1 Medical costs

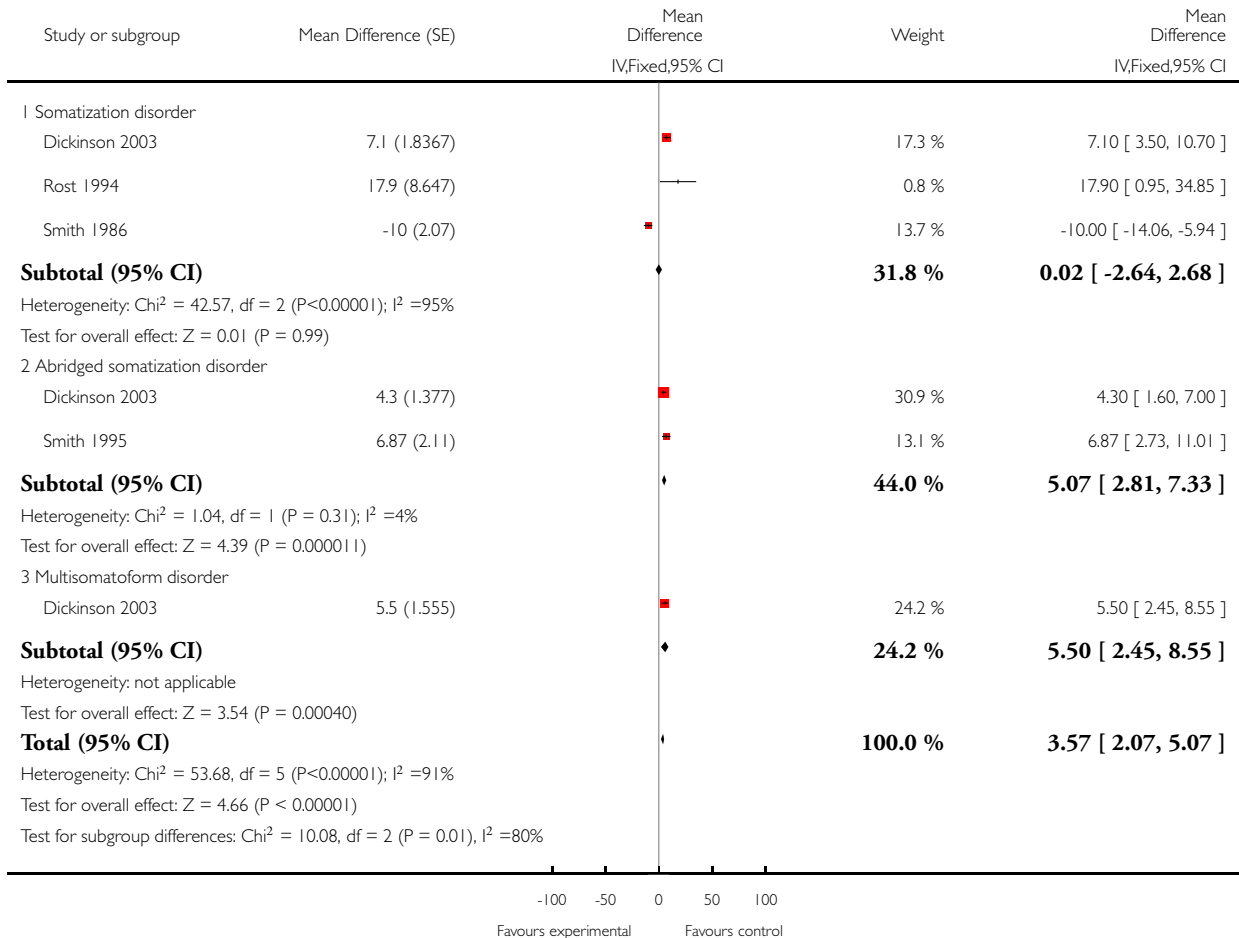


Analysis 3.2. Comparison 3 Consultation letter versus CAU with study results imputed for SD, Outcome 2 Physical functioning.

Review: Consultation letters for medically unexplained physical symptoms in primary care

Comparison: 3 Consultation letter versus CAU with study results imputed for SD

Outcome: 2 Physical functioning



ADDITIONAL TABLES

Table 1. Criteria list for the assessment of methodological quality of included studies

Item ID	Description	Implementation
Patient selection		NOTE: All criteria were scored yes (+), no (-) or don't know (?)
1	Was an adequate method of randomization applied?	A random (unpredictable) allocation sequence must have been applied. Methods of allocation based on date of birth, date of admission, hospital numbers, or alternation are not considered to be appropriate
2	Was the treatment allocation concealed?	Allocation should have been performed by an independent person who is not responsible for determining eligibility for inclusion. This person has no information about the patients included in the trial and has no influence on the allocation sequence or the decision about eligibility for inclusion
3	Was there an acceptable pre-randomization dropout?	Pre-randomization dropout rate was less than 20% after selection on clear criteria
Interventions		
4	Were the patients blinded for the intervention?	Adequate information about blinding must have been provided.
5	Were the caregivers blinded for the intervention?	Adequate information about blinding must have been provided.
Outcome measurement		
6	Was the outcome assessor blinded for the intervention?	Adequate information about blinding must have been provided.
7	Was the drop-out/loss to follow-up rate described and acceptable?	Included patients who did not complete the follow-up period or were not included in the analysis must have been described. If the percentage of drop-outs and loss to follow-up is < 20% for short-term follow-up and < 30% for long-term follow-up, and loss to follow-up does not lead to substantial bias, a '+' is scored. (N.B. these percentages are arbitrary, and not supported by empirical evidence)
8	MUPS were assessed with validated questionnaires and/or structured interviews	
Statistics		

Table 1. Criteria list for the assessment of methodological quality of included studies (Continued)

9	Did the analysis include an intention-to-treat analysis?	For all randomized patients, the most important moments of effect measurement should have been reported/analyzed (minus missing values), irrespective of non-compliance and co-interventions
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APPENDICES

Appendix I. MEDLINE, EMBASE and CENTRAL Search Strategies

OID MEDLINE was searched as follows:

1. exp Somatoform Disorders/
(*somatoform disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/*)
2. Psychophysiological Disorders/
3. Psychosomatic Medicine/
4. somati#ation.ti,ab.
5. somatoform.ti,ab.
6. hypochondriasis.ti,ab.
7. neurasthen\$.ti,ab.
8. conversion disorder\$.ti,ab.
9. psychophysiologic\$.ti,ab.
10. psychosomat\$.ti,ab.
11. psychogen\$.ti,ab.
12. (non organic\$ or nonorganic\$).ti,ab.
13. (unexplain\$ adj1 medical\$).ti,ab.
14. (unexplain\$ adj1 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
15. ((non specific or nonspecific) adj2 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
16. ((unexplain\$ or inexpl\$) and (health\$ or medical\$ or physical\$) and (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
17. frequent\$ attend\$.ti,ab.
18. (high utilis\$ or high utiliz\$).ti,ab.
19. or/1-18
20. (functional somatic adj2 (sympt\$ or syndr\$)).ti,ab.
21. Fibromyalgia/
22. fibromyalgi\$.ti,ab.
23. chronic widespread pain.ti,ab.
24. Fatigue Syndrome, Chronic/
25. fatigue syndrome.ti,ab.
26. ((non cardiac or noncardiac or non specific or nonspecific) adj2 chest pain).ti,ab.
27. NCCP.ti,ab.
28. Irritable Bowel Syndrome/
29. (IBS or (irritable bowel syndrome\$)).ti,ab.
30. multiple chemical sensitivity.mp.
31. idiopathic environmental intolerance.ti,ab.
32. Premenstrual Syndrome/
33. premenstrual adj2 (syndrome\$ or tension\$).ti,ab.
34. ((non ulcer nonulcer or functional) adj2 dyspepsia).ti,ab.

35. exp Cumulative Trauma Disorders/
cumulative trauma disorders/ or carpal tunnel syndrome/ or ulnar nerve compression syndromes/ or cubital tunnel syndrome/
36. cumulative trauma disorder\$.ti,ab.
37. repe\$ strain injur\$.ti,ab.
38. ((tension type or idiopathic or psychogenic) adj2 headache\$).ti,ab.
39. exp Temporomandibular Joint Disorders/
(temporomandibular joint disorders/ or temporomandibular joint dysfunction syndrome/)
40. ((temporomandibular joint or TMJ) adj2 (disease\$ or disorder\$ or dysfunction\$)).ti,ab.
41. or/20-40
42. 19 or 41
43. interdisciplinary communication.mp.
44. multidisciplinary communication.ti,ab.
45. exp Correspondence as Topic/
correspondence as topic/ or electronic mail/
46. correspondence.ti,ab.
47. Letter/
48. letter\$.ti,ab.
49. exp "Referral and Consultation"/
("referral and consultation"/ or ethics consultation/ or gatekeeping/ or physician self-referral/ or remote consultation/)
50. (recommendation or referral or consultation).ti,ab.
51. case management.mp.
52. liaison.ti,ab.
53. psychiatri\$ consult\$.ti,ab.
54. collaborative intervention\$.ti,ab.
55. specialist consultation\$.ti,ab.
56. or/43-55
57. randomized controlled trial.pt.
58. controlled clinical trial.pt.
59. randomi#ed.ti,ab.
60. placebo\$.tw.
61. trial\$.ti,ab.
62. randomly.ab.
63. (clinic\$ adj3 (trial\$ or study or studies\$)).ti,ab.
64. ((singl\$ or doubl\$ or tripl\$) adj (blind\$ or mask\$ or dummy\$)).ti,ab.
65. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
66. or/57-65
67. exp animals/ not humans.sh.
68. 66 not 67
69. 68 and 42
- Search terms for Consultation-Liaison Psychiatry and Primary Care:
70. (consultation liaison adj2 psychiatr\$).ti,ab.
71. C-L psychiatr\$.ti,ab.
72. Primary health care/
73. Family practice/
74. ((general or family) adj1 (practice\$ or practitioner\$)).ti,ab.
75. (primary care or primary healthcare or primary health care or primary health service\$).ti,ab.
76. (family adj (medic\$ or doctor\$ or physician\$ or health\$)).ti,ab.
77. (70 or 71) and (72 or 73 or 74 or 75 or 76)
78. 77 and 68

Medline In-Process Current Week (2009-08-17)

1. somati#ation.ti,ab.
2. somatoform.ti,ab.

3. hypochondriasis.ti,ab.
4. neurasthen\$.ti,ab.
5. conversion disorder\$.ti,ab.
6. psychophysiology\$.ti,ab.
7. psychosomat\$.ti,ab.
8. psychogen\$.ti,ab.
9. (non organic\$ or nonorganic\$).ti,ab.
10. (unexplain\$ adj1 medical\$).ti,ab.
11. (unexplain\$ adj1 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
12. ((non specific or nonspecific) adj2 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
13. ((unexplain\$ or inexpl\$) and (health\$ or medical\$ or physical\$) and (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
14. frequent\$ attend\$.ti,ab.
15. (high utilis\$ or high utiliz\$).ti,ab.
16. or/1-15
17. (functional somatic adj2 (sympt\$ or syndr\$)).ti,ab.
18. fibromyalgi\$.ti,ab.
19. chronic widespread pain.ti,ab.
20. fatigue syndrome.ti,ab.
21. ((non cardiac or noncardiac or non specific or nonspecific) adj2 chest pain).ti,ab.
22. NCCP.ti,ab.
23. (IBS or irritable bowel syndrome\$).ti,ab.
24. multiple chemical sensitivity.ti,ab.
25. idiopathic environmental intolerance.ti,ab.
26. (premenstrual adj2 (syndrome\$ or tension\$)).ti,ab.
27. ((non ulcer nonulcer or functional) adj2 dyspepsia).ti,ab.
28. cumulative trauma disorder\$.ti,ab.
29. repe\$ strain injur\$.ti,ab.
30. ((tension type or idiopathic or psychogenic) adj2 headache\$).ti,ab.
31. ((temporomandibular joint or TMJ) adj2 (disease\$ or disorder\$ or dysfunction\$)).ti,ab.
32. or/17-31
33. interdisciplinary communication.ti,ab.
34. multidisciplinary communication.ti,ab.
35. correspondence.ti,ab.
36. letter\$.ti,ab.
37. (recommendation or referral or consultation).ti,ab.
38. case management.ti,ab.
39. liaison.ti,ab.
40. psychiatri\$ consult\$.ti,ab.
41. collaborative intervention\$.ti,ab.
42. specialist consultation\$.ti,ab.
43. or/33-42
44. randomi#ed.ti,ab.
45. placebo\$.tw.
46. trial\$.ti,ab.
47. randomly.ab.
48. (clinic\$ adj3 (trial\$ or study or studies\$)).ti,ab.
49. ((singl\$ or doubl\$ or tripl\$) adj (blind\$ or mask\$ or dummy\$)).ti,ab.
50. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
51. or/44-50
52. 51 and 43 and (32 or 16)
- Search terms for Consultation-Liaison Psychiatry and Primary Care:
53. (consultation liaison adj2 psychiatr\$).ti,ab.
54. C-L psychiatr\$.ti,ab.

55. ((general or family) adj1 (practice\$ or practitioner\$)).ti,ab.
56. ((primary adj2 care) or primary healthcare or primary health care or primary health service\$).ti,ab.
57. (family adj (medic\$ or doctor\$ or physician\$ or health)).ti,ab.
58. (53 or 54) and (55 or 56 or 57)

Cochrane's CENTRAL Register of Controlled Trials (Issue 2, 2009) was searched as follows:

- #1. exp SOMATOFORM DISORDERS/
(*somatoform disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/*)
- #2. PSYCHOPHYSIOLOGIC DISORDERS/
- #3. PSYCHOSOMATIC MEDICINE/
- #4. somatization or somatisation
- #5. somatoform
- #6. hypochondriasis
- #7. neurasthen*
- #8. conversion NEAR/2 disorder*
- #9. psychophysiol*
- #10. psychosomat*
- #11. psychogen*
- #12. (non NEAR/2 organic*) or nonorganic*
- #13. unexplain* NEAR/2 (medical* or sympt* or problem* or condition* or complain*)
- #14. (non NEAR/2 specific) NEAR/2 (sympt* or problem* or condition* or complain*)
- #15. (nonspecific) NEAR/2 (sympt* or problem* or condition* or complain*)
- #16. ((unexplain* or inexpl*) and (health* or medical* or physical*) and (sympt* or problem* or condition* or complain*))
- #17. frequent* NEAR/2 attend*
- #18. (high NEAR/2 utilis*) or (high NEAR/2 utiliz*)
- #19. (*#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18*)
- #20. (functional NEXT somatic) NEAR sympt*
- #21. (functional NEXT somatic) NEAR syndr*
- #22. FIBROMYALGIA/
- #23. fibromyalgia*
- #24. chronic NEAR widespread NEAR pain
- #25. FATIGUE SYNDROME, CHRONIC/
- #26. fatigue NEAR/2 syndrome
- #27. (non NEXT cardiac) NEAR (chest NEXT pain)
- #28. noncardiac NEAR (chest NEXT pain)
- #29. (non NEXT specific) NEAR (chest NEXT pain)
- #30. nonspecific NEAR (chest NEXT pain)
- #31. NCCP.
- #32. IRRITABLE BOWEL SYNDROME/
- #33. irritable NEXT bowel NEXT syndrome*
- #34. IBS
- #35. MULTIPLE CHEMICAL SENSITIVITY/
- #36. multiple NEXT chemical NEXT sensitivity
- #37. idiopathic NEXT environmental NEXT intolerance
- #38. PREMENSTRUAL SYNDROME/
- #39. premenstrual NEAR (syndrome* or tension*)
- #40. (non NEXT ulcer) NEAR dyspepsia
- #41. (nonulcer or functional) NEAR dyspepsia
- #42. CUMULATIVE TRAUMA DISORDERS/
(*cumulative trauma disorders/ or carpal tunnel syndrome/ or ulnar nerve compression syndromes/ or cubital tunnel syndrome/*)
- #43. cumulative NEXT trauma NEXT disorder*
- #44. repe* NEXT strain NEXT injur*
- #45. (tension NEXT type) NEAR headache

#46. (idiopathic or psychogenic) NEAR headache*

#47. exp TEMPOROMANDIBULAR JOINT DISORDERS/
(*temporomandibular joint disorders/ or temporomandibular joint dysfunction syndrome/*)

#48. TMJ NEAR (disease* or disorder* or dysfunction*)

#49. (temporomandibular NEXT joint) NEAR (disease* or disorder* or dysfunction*)

#50. (#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48# or #49)

#51. #50 or 19.

#52. INTERDISCIPLINARY COMMUNICATION/

#53. interdisciplinary NEXT communication

#54. multidisciplinary NEXT communication

#55. exp CORRESPONDENCE AS TOPIC/
correspondence as topic/ or electronic mail/

#56. (correspondence or letter*):ti,ab

#57. exp "REFERRAL AND CONSULTATION"/
(*"referral and consultation"/ or ethics consultation/ or gatekeeping/ or physician self-referral/ or remote consultation/*)

#58. (recommendation or referral or consultation)

#59. CASE MANAGEMENT/

#60. case NEXT management

#61. liaison

#62. psychiatri* NEXT consult*

#63. collaborative NEXT intervention*

#64. specialist NEXT consultation*

#65. (#52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64)

66. #65 and #51

OVID EMBASE was searched as follows:

1. Somatoform Disorder/
(*somatoform disorder/ or body dysmorphic disorder/ or cardiac anxiety/ or conversion disorder/ or delusional pregnancy/ or hypochondriasis/ or masked depression/ or psychogenic pain/ or somatic delusion/ or somatization/*)
2. Psychosomatics/
3. Neurasthenia/
4. somati#ation.ti,ab.
5. somatoform.ti,ab.
6. hypochondriasis.ti,ab.
7. neurasthen\$.ti,ab.
8. conversion disorder\$.ti,ab.
9. psychophysiologic\$.ti,ab.
10. psychosomat\$.ti,ab.
11. psychogen\$.ti,ab.
12. (non organic\$ or nonorganic\$).ti,ab.
13. (unexplain\$ adj1 medical\$).ti,ab.
14. (unexplain\$ adj1 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
15. ((non specific or nonspecific) adj2 (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
16. ((unexplain\$ or inexpl\$) and (health\$ or medical\$ or physical\$) and (sympt\$ or problem\$ or condition\$ or complain\$)).ti,ab.
17. frequent\$ attend\$.ti,ab.
18. (high utilis\$ or high utiliz\$).ti,ab.
19. or/1-18
20. (functional somatic adj2 (sympt\$ or syndr\$)).ti,ab.
21. Fibromyalgia/
22. fibromyalgi\$.ti,ab.
23. chronic widespread pain.ti,ab.
24. Fatigue Syndrome, Chronic/

25. fatigue syndrome.ti,ab.
26. ((non cardiac or noncardiac or non specific or nonspecific) adj2 chest pain).ti,ab.
27. NCCP.ti,ab.
28. Irritable Colon/
29. (IBS or (irritable bowel syndrome\$)).ti,ab.
30. multiple chemical sensitivity.mp.
31. idiopathic environmental intolerance.ti,ab.
32. Premenstrual Syndrome/
33. premenstrual adj2 (syndrome\$ or tension\$).ti,ab.
34. ((non ulcer nonulcer or functional) adj2 dyspepsia).ti,ab.
35. exp Cumulative Trauma Disorders/
(*cumulative trauma disorder/ or carpal tunnel syndrome/ or iliotibial band friction syndrome/ or medial tibial stress syndrome/ or repetitive strain injury/ or tennis elbow/ or vibration syndrome/*)
36. cumulative trauma disorder\$.ti,ab.
37. repe\$ strain injur\$.ti,ab.
38. ((tension type or idiopathic or psychogenic) adj2 headache\$).ti,ab.
39. Temporomandibular Joint Disorders/
40. ((temporomandibular joint or TMJ) adj2 (disease\$ or disorder\$ or dysfunction\$)).ti,ab.
41. or/20-40
42. 19 or 41
43. interdisciplinary communication.mp.
44. multidisciplinary communication.ti,ab.
45. Patient referral/
46. case management.mp.
47. psychiatri\$ consult\$.ti,ab.
48. collaborative intervention\$.ti,ab.
49. specialist consultation\$.ti,ab.
50. ((consultation\$ or specialist\$ or physician\$ or psychiatri\$) and (letter\$ or correspondence or communication\$ or collaboration\$ or referral\$ or recommendation)).ti,ab.
51. Liaison psychiatry/
52. liaison.ti,ab.
53. or/43-52
54. major clinical study.de.
55. clinical article.de.
56. clinical trial.de.
57. controlled clinical trial.de.
58. controlled study.de.
59. randomized controlled trial.de.
60. double blind procedure.de.
61. single blind procedure.de.
62. randomization.de.
63. placebo.de.
64. prospective study.de.
65. comparative study.de.
66. follow up.de.
67. (randomi#ed or randomly).ti,ab.
68. ((singl\$ or doubl\$ or tripl\$) adj (blind\$ or mask\$ or dummy)).ti,ab.
69. placebo\$.tw.
70. (clinic\$ adj3 (trial\$ or study or studies\$)).ti,ab.
71. comparative stud\$.ti,ab.
72. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
73. or/54-72
74. ((animal or nonhuman) not (human and (animal or nonhuman))).de.

75. 73 not 74

76. 75 and 53 and 42

Search terms for Consultation-Liaison Psychiatry and Primary Care:

77. Liaison psychiatry/

78. (consultation liaison adj2 psychiatr\$.ti,ab.

79. C-L psychiatr\$.ti,ab.

80. Primary medical care/

81. General practitioner/

82. ((general or family) adj1 (practice\$ or practitioner\$)).ti,ab.

83. (primary care or primary healthcare or primary health care or primary health service\$).ti,ab.

84. (family adj (medic\$ or doctor\$ or physician\$ or health)).ti,ab.

85. (77 or 78 or 79) and (80 or 81 or 82 or 83 or 84)

86. 85 and 75

OID PsycINFO was searched as follows:

1. exp Somatoform Disorders/

(somatoform disorders/ or body dysmorphic disorder/ or exp conversion disorder/(conversion disorder/ or hysterical paralysis/ or hysterical vision disturbances or pseudocyesis/ or hypochondriasis/ or neurasthenia/ or neurodermatitis/ or somatization disorder/ or somatoform pain disorder/)

2. Psychosomatic medicine/

3. somati#ation.tw.

4. somatoform.tw.

5. hypochondria\$.tw.

6. neurasthen\$.tw.

7. conversion disorder\$.tw.

8. psychophysiol\$.mp.

9. psychosomat\$.tw.

10. psychogen\$.tw.

11. (non organic\$ or nonorganic\$).tw.

12. (unexplain\$ adj1 medical\$).tw.

13. (unexplain\$ adj1 (sympt\$ or problem\$ or condition\$ or complain\$)).tw.

14. ((non specific or nonspecific) adj2 (sympt\$ or problem\$ or condition\$ or complain\$)).tw.

15. ((unexplain\$ or inexpl\$) and (health\$ or medical\$ or physical\$) and (sympt\$ or problem\$ or condition\$ or complain\$)).tw.

16. frequent\$ attend\$.tw.

17. (high utilis\$ or high utiliz\$).tw.

18. or/1-17

19. (functional somatic adj2 (sympt\$ or syndr\$)).tw.

20. Fibromyalgia/

21. fibromyalgi\$.tw.

22. chronic widespread pain.tw.

23. Chronic Fatigue Syndrome/

24. fatigue syndrome.tw.

25. ((non cardiac or noncardiac or non specific or nonspecific) adj2 chest pain).tw.

26. NCCP.tw.

27. Irritable Bowel Syndrome/

28. (IBS or irritable bowel syndrome\$).tw.

29. multiple chemical sensitivity.tw.

30. idiopathic environmental intolerance.tw.

31. Premenstrual Syndrome/

32. premenstrual adj2 (syndrome\$ or tension\$).tw.

33. ((non ulcer or nonulcer or functional) adj2 dyspepsia).tw.

34. cumulative trauma disorder\$.tw.

35. repe\$ strain injur\$.tw.

36. ((tension type or idiopathic or psychogenic) adj2 headache\$).tw.

37. Musculoskeletal disorders/
38. ((temporomandibular joint or TMJ) adj2 (disease\$ or disorder\$ or dysfunction\$)).tw.
39. or/19-38
40. 19 or 39
41. Interdisciplinary treatment approach/
42. ((multidisciplinary or interdisciplinary) adj treatment approach).tw.
43. interdisciplinary communication.tw.
44. multidisciplinary communication.tw.
45. correspondence.tw.
46. Profesional referral/
47. (recommendation or referral or consultation).tw.
48. ((consultation\$ or specialist\$ or physician\$ or psychiatri\$) aand (letter\$ or correspondence or communication\$ or collaboration\$ or referral\$ or recommendation\$)).tw.
49. case management.mp.
50. liaison.tw.
51. psychiatri\$ consult\$.tw.
52. collaborative intervention\$.tw.
53. specialist consultation\$.tw.
54. Interdisciplinary Treatment Approach/
55. exp Professional consultation
(*professional consultation or consultation liaison psychiatry/*)
56. or/41-55
57. treatment effectiveness evaluation.de.
58. clinical trials.de.
59. placebo.de.
60. treatment outcomes.de.
61. psychotherapeutic outcomes.de.
62. mental health program evaluation.de.
63. evaluation.de.
64. followup studies.de.
65. random\$.tw.
66. placebo\$.tw.
67. comparative stud\$.tw.
68. (clinical adj3 trial\$).tw.
69. (research adj3 design).tw.
70. (evaluat\$ adj3 stud\$).tw.
71. (prospectiv\$ adj3 stud\$).tw.
72. ((singl\$ or doubl\$ or tripl\$) adj3 (blind\$ or mask\$ or dummy)).tw.
73. or/8-22
74. (animal NOT (animal and (human or inpatient or outpatient))).po.
75. 73 not 74
76. 75 and 56 and 40
- Search terms for Consultation-Liaison Psychiatry and Primary Care:
77. Consultation liaison psychiatry/
78. (consultation liaison adj2 psychiatr\$).tw.
79. C-L psychiatr\$.ti,ab.
80. Primary health care/
81. General practitioners/
82. Family physicians/
83. ((general or family) adj1 (practice\$ or practitioner\$)).ti,ab.
84. (primary care or primary healthcare or primary health care or primary health service\$).ti,ab.
85. (family adj (medic\$ or doctor\$ or physician\$ or health)).ti,ab.
86. (77 or 78 or 79) and (80 or 81 or 82 or 83 or 84 or 85)

Appendix 2. CCDAN-CTR Search Strategies

The CCDAN-CTR References Register was searched using the following terms:

Free Text = ("medically unexplained" or "unexplained medical*" or "unexplained symptom*" or "unexplained physical" or MUS or MUPS or "frequent attend*" or "high utili*" or "high-utili*" or psychosomatic* or somatisation or somatization or somatoform or hypochondriasis or neurathen* or "conversion disorder*" or psychophysiologic* or psychosomat* or psychogen* or "non organic*" or non-organic*" or "nonorganic*" or "functional somatic*" or fibromyalgia* or "chronic widespread pain" or "fatigue syndrome" or ((("non cardiac" or non-cardiac or noncardiac or "non specific" or "non-specific" or nonspecific) and "chest pain") or NCCP or IBS or "irritable bowel syndrome" or "multiple chemical sensitivit*" or "idiopathic environmental intolerance*" or "premenstrual syndrome" or "premenstrual tension" or "non ulcer dyspepsia" or non-ulcer dyspepsia" or "nonulcer dyspepsia" or "functional dyspepsia" or "cumulative trauma disorder*" or "repe* strain injur*" or "tension type headache*" or "tension-type headache*" or "idiopathic headache*" or "psychogenic headache*" or "temoromandibular joint disorder*" or TMJ or ((("non specific" or "non-specific" on nonspecific or unexplain* or inexpl*) and (symp* or problem* or complain* or condition*)) AND

Free Text = ("psychiatric consultation*" or "collaborative intervention*" or "specialist consultation*" or "case management" or liaison or correspondence or letter* or referral* or "interdisciplinary communication" or "multidisciplinary communication" or recommendation* or consultation*)

The CCDAN-CTR Studies Register was searched using the terms:

consultation" or "collaborative intervention" or "case management" or liaison or correspondence or letter or referral or communication) AND

"medically unexplained" or somatoform or somatization or psychosomatic or somatic or "frequent attend*" or "high utili*" or "conversion disorder" or neurasthenia or fibromyalgia or "fatigue syndrome" or "chronic fatigue" or hypochondriasis or "premenstrual dysphoric disorder" or "premenstrual syndrome" or "premenstrual symptoms" or "irritable bowel syndrome" or IBS"

CONTRIBUTIONS OF AUTHORS

- R. Hoedeman: designing and writing the concept of the protocol and review, screening and selecting the papers, extracting the data, assessing the quality of the studies, entering the data into RevMan, interpreting the data, securing funding for the review.
- A.H. Blankenstein: co-author of the protocol and review, screening and selecting the papers, extracting the data, assessing the quality of the studies, interpreting the data.
- C.M. van der Feltz-Cornelis: general advice on the review, third reviewer assessing eligibility for inclusion and quality assessment of the studies.
- B. Krol: general advice on the review, providing methodological advice on the interpretation of the data
- R.E. Stewart: extraction of the data, configuring and presenting the data, providing statistical support
- J.J.W. Groothoff: responsible for the scientific quality of the review

DECLARATIONS OF INTEREST

C.M. van der Feltz-Cornelis is first author of one of the included studies. She did not participate in the quality assessment of her own study. She had a limited role in the quality assessment of the other studies, for which the final assessment and final decisions were all taken by the first two authors.

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Internal sources

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- Dutch Ministry of Social Affairs and Employment provided a grant as part of the Knowledge Infrastructure in OHS program, Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We performed the protocol as described. We sub-divided medical consumption into medical outpatient care and medical inpatient care since, due to the nature of the intervention, the effects on outpatient care and inpatient care were expected to be different. We added perceived health as a secondary outcome. This outcome is included in measurement instruments to assess functioning (especially RAND and SF-36), but also measures other aspects than physical and mental (role) functioning. To make this distinction we added this outcome.

In this review we assessed the methodological quality according to The Cochrane Collaboration's Risk of Bias tool ([Higgins 2008a](#)) and not with the Tulder checklist ([Van Tulder 1997](#); [Van Tulder 2003](#)) as indicated in our protocol. This was done on advice of the peer reviewers, to enhance the comparability of the review. We extended the checklist with three criteria: assessing MUPS with validated instruments; complete description of baseline characteristics and acceptable pre-randomization dropout.

We also added some references with regard to what is known about the relationship between MUPS and sickness absence.

INDEX TERMS

Medical Subject Headings (MeSH)

*Interview, Psychological; *Medical Records; Anxiety [diagnosis; psychology]; Case Management [organization & administration]; Cross-Over Studies; Depression [diagnosis; psychology]; Health Services Needs and Demand [economics; statistics & numerical data]; Patient-Centered Care; Primary Health Care; Psychiatry; Randomized Controlled Trials as Topic; Referral and Consultation [*organization & administration]; Somatoform Disorders [*diagnosis; economics; psychology; *therapy]

MeSH check words

Humans